

## Phenolic compounds as nutraceuticals or functional food ingredients

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**Abstract:** *Background:* Nowadays, the functional foods represent one the most promising, interesting and innovative areas in the food industry. Various components are being added to foods in order to render them functional. *Methods:* One example of these components are plant naturally occurring phenolic compounds, which are associated with a high antioxidant capacity and thus with benefits in relation to human health. *Results:* However, despite the huge number of scientific studies and patents on this topic and their natural presence in foods, namely in the ones from plant origin, there are still few marketable products enriched with these compounds. The commercialization of this type of functional products needs to go through various regulations, proving that they are safe and present the ascribed health benefits, conquering the target audience. In this review the growing interest of industry and consumers' appetite for functional foods and nutraceuticals is highlighted, focusing especially phenolic compounds. *Conclusion:* Although several published works show the multitude of bioactive properties of these compounds, ensuring their use as bioactive ingredients in food, they present inherent stability issues needing to be solved. However, considerable research is presently ongoing to overcome this problem, making viable the development of new products to be launched in the market.

**Keywords:** Phenolic compounds; nutraceuticals; functional foods; health benefits; consumers.

## 1. INTRODUCTION

The scientific community and the food industry have developed an increasing interest for functional and nutraceutical properties of some nutrients and natural compounds, in view of their incorporation in added-value foodstuffs. These enrichments can use natural sources from plant, mushroom or animal origin, but also synthetic compounds with improved biological activities. Some examples of bioactive ingredients are vitamins, amino acids, fibers, fatty acids, and phenolic compounds (PC) [1]. The bioactive ingredients obtained from natural sources have been used since ancient times all over the world with the conviction that guarantee medicinal properties in fighting certain diseases [2,3].

Phenolic acids, flavonoids and stilbenes are some of the PC classes, widely distributed among medicinal herbs and dietary plants. These compounds present a broad range of bioactivities such as antioxidant, antimicrobial, anti-inflammatory, antitumoral and hepatoprotective effects. Some PC exhibit

high antioxidant activity as individual compounds, while others, depend on synergisms to undergo bioactive effects [4]. The antioxidant activity of these compounds is related with their chemical structure, generally depending on hydroxyl groups' number and position, glycosylation or other types of substitution [5]. Furthermore, PC are involved in the neutralization of reactive species that attack cell molecules and in several diseases prevention related to oxidative and nitrosative stress such as cancer, cardiovascular diseases, atherosclerosis, neurological disorders, hypertension, and diabetes mellitus, among others [4].

There are also many studies describing the antifungal activity of PC, expressed through an interaction with the lipid bilayer of the fungi cell membrane (disruption of the membrane integrity or intercalation into cell wall and/or DNA - Deoxyribonucleic Acid) [6]. These compounds have also shown antimicrobial activity, by delaying or inhibiting the growth of pathogenic and/or toxin-producing microorganisms in food, as also by minimizing the incidence of foodborne diseases caused by food spoilage bacteria and fungi [7]. The numerous scientific studies with PC also described their anti-inflammatory properties [8,9]. During the inflammation process it is observed the formation of various reactive oxygen species (ROS) and reactive nitrogen species (RNS) that result in increased activity of pro-inflammatory agents. The PC have ability to reduce or prevent the prejudicial effects in human organism through the reduction of pro-inflammatory enzymes [10].

Cancer is a global concern which causes millions of deaths each year, even in the most developed countries [11]. Despite major advances in the treatment of patients with cancer these remain insufficient to reduce suffering and mortality [12]. In traditional medicine, the plants represent an important ally in the treatment of various diseases. Currently, natural compounds represent an important fraction in the composition of new anticancer drugs developed by the pharmaceutical industry [13,14]. Several studies have concluded that bioactive ingredients from plants may have anticancer effects in cell lines but also in murine models, including being more efficient than synthetic compounds [15]. There are several toxicity problems associated with the use of synthetic molecules in the treatment of cancer. Alternatively, some natural compounds isolated from plants can be administered without any side effect or toxicity to patients [15]. The potential antitumoral effects of PC have been intensively studied, both with tumor cell lines and by using *in vivo* models and human trials [15]. PC have shown the capacity to induce apoptosis by arresting cell cycle, regulate carcinogen metabolism and ontogenesis expression, inhibit DNA binding and cell adhesion, migration, proliferation or differentiation, and block signaling pathways [16]. Additionally, PC have been intensively studied in regard to their hepatoprotective capacity against chemically induced damage, either *in vivo* or *in vitro*. These compounds seem to overcome liver injuries often caused by oxidative reactions that promote lipid peroxidation in hepatic tissues; among these constituents, flavonoids and phenolic acids have received special attention for their high antioxidant activity supporting the observed hepatoprotective effects [17].

Due to their characteristics, foods rich in PC have been considered functional foods. Although the existence of earlier reports (1985-1999), a significant growing interest for this type of products, either from academia (through research articles and scientific reviews) or industry (through patents), was observed since 2000, indicating an increasing tendency (Figure 1).

In this review article, the sector of functional foods and nutraceuticals was analyzed, highlighting the particular case of the use of PC as bioactive ingredients, either in functional foods or in nutraceutical formulations. Examples of products already available in the market will be also given.

## 2. THE GROWING SECTOR OF FUNCTIONAL FOODS AND NUTRACEUTICALS

### 2.1. Definitions

The term "functional food" first appeared in the 80s in Japan in reference to food products enriched with special components that have beneficial physiological effects [18,19].

A food can be classified as "functional" if, beyond adequate nutritional effects, it demonstrates benefits in one or more target functions in the human body relevant to improve health and well-being and/or to reduce risk disease. These foods can be natural or unmodified, or foods to which a component has been added or removed by technological means. They can be naturally ingested in diet. Thus, functional foods can be classified as: 1) Non-altered products, foods which naturally contain a high level of nutrients/health promoting compounds (e.g. eggs with increased omega-3); 2) Fortified products, foods in which components content is increased (e.g. fruit juices fortified with vitamin C); 3) Enriched products, foods to which a component with certain benefits was added (e.g. margarine with plant sterol ester, pro and prebiotics); 4) Altered products, i.e. foods in which a specific component was removed or substituted (e.g. addition of fibers as fat releasers in meat or ice cream products) [20-22].

Presently there is no definition or legislation universally accepted for functional foods [23]. However, this is one of the most interesting and active research and innovation areas for the food industrial sector [24]. Its market share is growing worldwide, and new products are being continuously launched [19]. Some commercial products with beneficial health functions can be already found; among them the most demanded by the consumers are: probiotic liquid yogurt containing *Lactobacillus casei* Imunitass<sup>®</sup> cultures (brand Actimel<sup>®</sup> from Danone<sup>®</sup>, France), solid yogurt with *Bifidus ActiRegularis*<sup>®</sup> (brand Activia<sup>®</sup> from Danone<sup>®</sup>, France), snacks and cereal bars with natural fibers and extra minerals and vitamins (Snack brand Fibra<sup>®</sup> from Celigüeta<sup>®</sup>, Spain), dairy drink with *L. casei* Shirota (brand Yacult<sup>®</sup> from Yacult<sup>®</sup>, Japan) and yogurt containing pre- and probiotics and omega-3 (brand Vitality<sup>®</sup>, Müller<sup>®</sup>, Germany).

Among others, dairy products have many reported health benefits. They are widely consumed and appreciated by consumers and, thus, represent an important vehicle for functional foods development. Moreover, the dairy industry is considered one of the most important and dynamic sectors of the food industry. This sector is in permanent innovation trying to develop new products with added value. Accordingly, an increasing variety of new dairy products has been observed to satisfy consumer's demand for healthier products, including low-fat (e.g. skimmed and semi-skimmed milk) and the high-protein content ones [25].

In turn, nutraceuticals can be defined as diet supplements containing bioactive compounds or extracts, prepared from raw matrices and used in unit dosage forms such as tablets, capsules or liquids. Thus, the bioactive agent is in this case more concentrated, and otherwise, it cannot be obtained from the normal food intake to present positive physiological effects on the human body [26,27]. Nowadays, the

use of nutraceutical formulations in dietary supplements as a complement to prevent some diseases is very common [28]. Some authors classified nutraceuticals in traditional (substances naturally contained in foods) and non-traditional (substances added to foods by bio-engineering actions) [29]. Nutraceuticals concept is relatively recent, only appearing in the 90s, but consumer's demand for new, better and safer food products is pressing food industry for a constant innovation and product's offer increase [30].

The processing of nutraceuticals can follow four steps: pretreatment (includes homogenization, grinding, milling, maceration, and drying), extraction (in which the selection of a method depends of factors such as the source and type of bioactive compound to be extracted, desired recovery and operational requirements), isolation/purification, and encapsulation [31].

When processed under controlled conditions (i.e. under moderate temperature and pressure, and by avoiding light exposure), nutraceuticals can suffer minor deterioration, nevertheless extreme pH conditions or enzymes presence, typical of intestinal tract, can significantly affect their bioavailability [32,33].

It is a common pitfall the confusion between nutraceuticals and functional foods definition; even in the literature a nutraceuticals is defined as any food or part of it as long as their beneficial health and nutritional claims can be proved scientifically [28]. However, some authors consider nutraceuticals as components that are often consumed in unit dose forms such as tablets, capsules or liquids [27,34]. Sometimes nutraceuticals and functional foods are produced with the same ingredients but in different forms [35].

Nowadays, foods that indicate improvement of consumer's health have to go through a large control mainly in what concerns labeling information. The European Union (EU) is facing, since 2012, new legislation that requires a rigorous standard of scientific evidence for making health claims on foods, beverages and dietary supplements [34,36]. However, these foods are still not included in a specific food category [37]. On the other hand, in the United States of America (USA), Food and Drug Administration (FDA) defines the products categories depending on its characteristics obeying several safety issues, health claims, labelling and good manufacturing practices [38].

## **2.2. Hot scientific topics and consumer's increasing demand**

Behavioral and socio-demographic trends, particularly the existence of different eating habits motivate the existence of different national policies to promote public health. This, together with differences related to cultural traditions, constitute the main challenges towards the successful introduction of functional products on the market. Therefore, for a better consumer's acceptance a strong enlightenment about "functional food" concept is needed. Some studies have shown that cognitive, motivational and attitudinal determinants of consumer's acceptance of functional foods vary considerably in different countries [39]. However, there has been a huge change in eating habits, i.e., in addition to the nutritional and sensory properties, food seems to play an important role in health maintenance and disease prevention [40,41]. Therefore, functional foods have gained prominence, becoming its development a hot research area for both academia and industry [36].

Functional foods have been growing in the market over time. Some entities, like researchers and professionals, agree that the market for functional foods is achieving a raising growth worldwide

[39,40,42]. Their global market was estimated at about 625 billion dollars in 2012 [43], being the three main markets represented by Japan followed by the USA and finally EU. These three markets contribute to 90% of total sales [19]. Apart from its pioneer role (functional foods started to be a reality in this country), Japan is also the strongest market worldwide; in only 10 years (1988-1998) more than 1700 functional food products were released [19,44]. This market showed an average growth rate of 9.6% per year during the 90s, and their related industry was estimated to a turnover of approximately 12 billion dollars in 2003 [39].

The USA has the second largest market for functional foods, with a turnover of 10.5 billion dollars in 2003. In this country the market share for functional foods is around 2-3% and is constantly growing [39,40]. The ever-growing functional foods and drinks market increased 1.5 fold globally, reaching 24.2 billion dollars in 2010 and 29.8 billion dollars in 2014 [36].

Europeans still show some skepticism in relation to functional foods, partly due to suspected safety of these food products, but also because of their productive process [39]. The demand for functional foods in the EU varies due to food and cultural traditions, being higher in Northern Europe than in Mediterranean countries. United Kingdom (2.6 billion dollars), Germany (2.4 billion dollars), France (1.4 billion dollars) and Italy (1.2 billion dollars) stand as the main markets [19,39]. However, many other markets, such as Netherlands, Spain, Poland and Hungary, are experiencing high growth rates [199,39, 45-47].

In the EU, as well as in Japan, the market for functional foods is dominated by probiotics, and 370 products were launched worldwide in 2005 [48]. The lactic acid bacteria (LAB) and bifidobacteria are the most studied and used for new product development, for example in Italy, the most important product in functional food market is the called “health yogurt”; it represented in 2008 a growth rate of 6.3% per year, thus reaching 560 million euros of sales, corresponding to almost 4% of the whole Italian sector [19].

Functional foods have added benefits if compared to the traditional ones. The functionality of these foods is derived from the presence of bioactive ingredients. Typically, the functional ingredients incorporated into foods aimed at prevent some chronic diseases, as well as promote better physical and psychic well-being; therefore, health concerns are the most significant factors influencing consumers. According with Arvanitoyannis & Houwelingen-Koukaliaroglou [49], people from different countries seek for different characteristics in food. Thus, Americans search primarily functional food for weight loss and cholesterol lowering, while EU, which comprises the major consuming countries, wants mainly health prevention food. In particular, United Kingdom consumes foods to promote bone and teeth health, Germany to enhance/stimulate the immunologic system and bone health; and lastly, in France, the functional foods are consumed to stimulate cholesterol lowering and generally increase resistance to disease.

### **2.3. Main bioactive ingredients and food sectors**

The acceptance of a specific functional ingredient is intimately related to consumer's knowledge of its beneficial health effects. Thus, the functional ingredients known since a longer period, such as minerals, vitamins, fibers, and fatty acids reach considerably higher acceptance rates than the newer ones,

such as PC. In this case, consumers do not recognize the health benefits associated to this last group [22,25].

Vitamins and minerals are defined as nutrients and have recommended ingesting doses in order to produce the desired effect [50,51]. Vitamins are complex organic substances that are required in small quantities for a healthy body. With the exception of vitamin D, all other vitamins are not produced by the organism, having to be obtained through the diet. Vitamins play important biological functions, such as in the role of *co-factors* in enzymatic activity, as antioxidants or as *pro-hormone* [49]. Milaneschi et al [52] described that there is a correlation between vitamin E and the onset of depression in the elderly. This study was conducted with 531 women and 432 men aged from 65 years, being found a direct relationship between 25-hydroxyvitamin D deficiency and depression [25]. Dietary fibers are defined as non-digestible carbohydrates that are present in vegetal sources. The fibers can be classified as water soluble or insoluble, and may alter the nature of the gastrointestinal tract contents, changing the way nutrients and chemicals are absorbed. Examples such inulin and several other oligosaccharides stimulate bifidobacteria growth, increasing gut health (decreased intestinal transit) and immunity. Minerals are essential to body function, since they are involved in metabolic processes such as muscle contraction, nerve impulses transmission, water maintenance, acid-base balance, and catalysis of other biological reactions [49].

PC, compounds naturally present in plants, are among the most interesting bioactives due to its great antioxidant capacity associated with benefits in relation to human health, namely in the prevention of some common diseases [53]. This type of compounds have been widely studied in recent years, and further incorporated into different food matrices in order to render them functional [54,55].

Currently, food industry has developed different fortified food products to meet consumer's demands, who are increasingly concerned with their feeding habits. Therefore, new functional food products have been developed by introducing the active ingredient at the correct dosage, and without changing organoleptic and texture properties, as appreciated by the consumers [30,56].

Functional foods have been developed in virtually all food categories. Functional cereal components such as beta-glucan (mainly from oat and barley), have been used in dairy bakery industries to manufacture low-fat ice creams [57]. The bakery products still represent a small share in the functional foods industry (just over 13% in 2000s), comparatively with dairy products, which holds the largest share of the functional food market [22,40]. However, a growth in this sector has been observed, and there are some successful examples in the market. This is the case of Unilever® that produced in 2003 the "Blue Band Goede Start®" as the first white bread enriched with functional elements (fiber, vitamins B1, B3 and B6, iron, zinc and inulin), only available on whole wheat bread [58].

Eggs, a fatty acids rich food highly appreciated by consumers, are another example that raised interest in the food industry to make them functional. In the United Kingdom, the Freshlay Foods® produced the VITA Eggs®, described as eggs enriched with omega-3 fatty acids conjunctly with antioxidants and other vitamins (D, E, B12 and folic acid). Also in Belgium, there is a similar successful case: the Columbus® by Belovo®, eggs enriched in omega-3 and vitamin E, currently exported all over the world and whose annual production is estimated to be over 50 million [22].

In EU, the market of non-alcoholic beverages enriched with vitamins (especially A, C and E), and other bioactive components, is still running at a modest scale. However, its growth is rising exponentially

bringing to market various highly appreciated products. In particular, drinks with soy and omega-3 (to lower cholesterol), drinks with lutein (to improve vision) and drinks with calcium and insulin (to improve health issues), can be cited as examples [59]. Germany is a successful representative of this food category mainly due to the success of ACE® drinks, with a sales income of many millions of dollars in the last decade [22]. Another example of success, especially for its great contribution to the Estonian economy, is the Largo® beverages (juices fortified with inulin, L-carnitine, vitamins, calcium and magnesium) [60]. Also functional liquid dairy products, including yogurts, are among the most succeeding products. These foods are usually enriched with pre- and/or probiotics in order to impart some beneficial functions in the body. This type of dairy products features an impressive growth of many millions of dollars throughout EU. In this area the most representative brands are Danone® and Unilever®, which have faced an exponential growth [22]. A widely known product is Benecol® a dairy beverage enriched with camelina oil as a source of fatty acids, in particular of the omega-3 type associated with cholesterol lowering. Functional butters are another example of products with great market expansion. Becel® pro activ, trade name owned by Becel® (Unilever®), is a well-known product to lower cholesterol, property related with the added plant stanol esters [61].

Several companies recognized worldwide, betting much of their investment in products referred as "healthier". Food companies such as Nestlé®, Danone® Group, Kraft Foods®, Unilever®, PepsiCo®, Coca-Cola®, and Heinz® are some of these examples. Recently, there has been also the promotion of some joint-ventures between food industries and pharmaceutical companies, because the cost and time of producing functional foods is lower than producing pharmaceutical products.<sup>22</sup>

Among all the functional food markets, the major product launches are: milk products, confectionery, bakery and baby foods.<sup>19,40</sup> The market of functional dairy products has grown rapidly due to the recognized large investment in research directed to the sector, which assured the development of new marketable products. Furthermore, many authors explain the great success of functional dairy products due to the good image consumers have of them [22,62].

### **3. PHENOLIC COMPOUNDS AS BIOACTIVE INGREDIENTS**

#### **3.1. Chemical and biological issues**

The PC are secondary metabolites of plants generally involved in the defense against ultraviolet radiation or aggression by pathogens [63], being the major antioxidants of our diet [64].

Their main dietary sources are fruits and plant-derived beverages such as fruit juices, tea, coffee and red wine. Vegetables, cereals, chocolate, and dry leguminous also contribute to the total PC intake [65,66]. The total dietary intake is about 1g/day, being much higher than that of all other known dietary antioxidants, about 10 fold higher than that of vitamin C and 100 fold higher than those of vitamin E and carotenoids [64,67].

In nature, PC are usually found conjugated to sugars and organic acids [66,68]. They can be classified according to two major types, flavonoids and non-flavonoids (Figure 2) and in different classes,

which depend on the number of phenol rings and on the structural elements linking these rings [68,69]. Nevertheless, there is still some controversy in associated to the classes of PC to be considered [70].

Flavonoid group, shares a common structural feature, consisting of 2 aromatic rings (A and B) bounded together by 3 carbon atoms that form an oxygenated heterocycle (ring C). It can be divided into six subclasses according to the type of involved heterocycle: flavonols, flavones, flavanols, flavanones, isoflavones and anthocyanins [69]. The individual differences within each group refer to variations in the number and arrangement of the hydroxyl groups, as well as in their extent of alkylation and/or glycosylation [66]. Among the various compounds, quercetin and catechins stand out as the most common ones.

Several studies have suggested that flavanols, flavones, and flavanones, the main flavonoids found in citrus fruits, occur at high concentration in the cocoa-rich products and dark chocolates, and are related to the reduction of cardiovascular disease risk [71,72].

The non-flavonoids group is composed by phenolic acids, stilbenes and lignans [69]. Phenolic acids are found abundantly in foods and can be divided into two classes: hydroxybenzoic and hydroxycinnamic acids. The hydroxybenzoic acid content in edible plants is generally low, with the exception of certain red fruits and onions. Normally these fruits have large amounts of gallic acid. The hydroxycinnamic acids are more common than hydroxybenzoic acids and consist mainly of coumaric, caffeic, ferulic and rosmarinic acids [66,69]. Stilbenes are not typically ingested in large quantities since plants only synthesized them if subjected to episodes of infection or injury. However, grapes and wine contain significant amounts of resveratrol, making this stilbene one of the most studied ones [56]. Lignans, such as secoisolariciresinol, are considered to be phytoestrogens. Its richest dietary source is linseed, which contains secoisolariciresinol and low quantities of matairesinol [59].

Several studies have reported the antioxidant potential of certain PC being apigenin, quercetin, kaempferol, myricetin, luteolin, isorhamnetin, caffeic and *p*-coumaric acids the most cited (Table 1) [73,74]. Yeh & Yen [75] demonstrated that administration of phenolic acids, mainly gallic acid, in rats induces phase II hepatic phenol sulfotransferases (PSTs) and increase plasma antioxidant capacity. Another study administrated an anthocyanin rich extract, obtained from the cones of *Abies koreana* E.H.Wilson, to male rats and proved that it increased plasma antioxidant capacity [76]. Flavan-3-ols, mostly catechins, were detected in high amounts in rat blood, and were able to suppress the occurrence of gastric lesions in rats [77]. These compounds showed high antioxidant activity leading to a great protection of endothelial cells from oxidative injury [78]. Several studies were conducted to prove the antioxidant properties of flavones. The apigenin revealed strongly antioxidant activity *in vitro* and *in vivo* assays through neuroprotective effects against oxidative stress [79,80]. Another flavone, kaempferol, also revealed high antioxidant activity, being recommended as a good natural antioxidant due to its tendency to donate electrons and, therefore, stabilizing food products [81].

The most studied PC in terms of antifungal properties are phenolic acids, flavonoids and stilbenes [6] presented in Table 2. The antimicrobial activity of phenolic acids was reported by various authors which proved that chlorogenic, ferulic and gallic acids have the ability to inhibit the growth of different microorganisms such as *Staphylococcus aureus* and *S. epidermis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Listeria monocytogenes* [82-87]. The catechin, belonging to flavan-3-ols group, inhibited



the growth of various fungi and bacteria strains, such as *Candida albicans* [88], *Helicobacter pylori* [86] and *Escherichia coli* [87]. Also the flavanones, hesperetin and narigenin, showed strong antifungal and antibacterial effects against *S. aureus*, *C. albicans* and *Lactococcus lactis* [89-91]. Strong activity against *P. aeruginosa*, *Salmonella typhimurium*, *S. epidermis*, *Bacillus subtilis* and *Saccharomyces cerevisiae* was displayed by two examples of flavones, apigenin and luteolin [92,93]. Studies with flavonols (kaempferol and rutin) revealed their antibacterial activity against *Enterococcus faecalis* and *S. aureus* [94,95]. The antibacterial activity of genistein, an isoflavone, was studied against *Vibrio harveyi* [96], *Bacillus anthracis* [97], *Klebsiella pneumonia* and *Salmonella typhi* [98]. Finally, resveratrol, a stilbene, showed antibacterial activity against various bacteria such as *E. faecalis* [94], *Campylobacter* spp., *Arcobacter butzleri* [99], *S. cerevisiae*, *Aspergillus niger*, *Penicillium expansum* [100] and *H. pylori* [101], as also against *C. albicans* fungi [102].

Other studies demonstrated that PC possess anti-inflammatory activity (Table 3). Wang et al [103] reported the anti-inflammatory activity of hesperetin, a flavanone, and suggested that this PC was inhibitor of tumor necrosis factor  $\alpha$  and interleukin-6 in mouse macrophages. This activity was also verified by different authors for two important flavones, apigenin and luteolin. Funakoshi-Tago et al [104] demonstrated that apigenin effectively inhibited carrageenan-induced inflammation in murine model through inhibition NF- $\kappa$ B transcriptional activation mechanism. Luteolin was described as having the ability to inhibit tumor necrosis factor  $\alpha$  and NF- $\kappa$ B transcriptional activation under *in vivo* assays [104,105], to reduce nitric oxide synthase expression *in vitro* [106] and significantly alleviated neurological deficit *in vivo* suppressed edema after ischemic stroke due the decreased expression of several molecules involved in inflammatory processes [107]. The potent anti-inflammatory effect of luteolin was also described, by interfering essentially in the heat shock protein 90 (Hsp90) secretion [108].

Table 4 represents some PC with proved antitumoral activity. Some authors have shown an inhibition of reductase activity in tumor cells by treating leukemic cell lines with gallic acid [109]. Another study also demonstrated the efficiency of this acid against glioma cell lines, by decreasing cell viability, proliferation and angiogenesis [110]. Other authors reported that by inducing apoptosis and activating caspases, the gallic acid also had efficient effects on lung cancer cell lines. In a study with murine models it was demonstrated the same capability of reducing tumor growth [111]. Some authors demonstrated the anticancer effect of the anthocyanidins, cyaniding and delphinidin, against colorectal carcinoma [112]. In particular, delphinidin inhibited cell growth and decreased tumor size [113]. *In vivo* assays revealed that catechin, a flavan-3-ol, inhibited tumor formation and increased the life span of the animals. In turn, *in vitro* tests have confirmed that this compound inhibited the migration of melanoma cells [114]. In a study conducted by Alshatwi [115] catechins proved to exhibit anticancer effects and induce apoptosis on the MCF-7 cancer cell line (breast cancer) without significant toxicity. Within the flavanone group, hesperetin could inhibit the cell growth and induce apoptosis resulting on inhibition of human mammary carcinoma cell lines [116]. Alshatwi et al [117] revealed that hesperetin exhibited *in vitro* anticancer activity against human cervical cancer cell lines through the reduction of cell viability and induction of apoptosis. Narigenin proved anti-proliferative and apoptotic effects through 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in skin carcinoma cells line (A431)

by inducing ROS generation and cell cycle arrest [118]. In flavone group, apigenin and luteolin are the most studied PC. The apigenin showed anti-mutagenic and apoptotic effects in human lymphoma cells line [119] and inhibited pancreatic cancer cell growth and migration [120]. On the other hand, luteolin exhibited pro-apoptotic activities in colorectal cancer cells [121] and demonstrated anticancer effect on human lung carcinoma cell line (NCI-H460) through Sirt1-mediated apoptosis and the inhibition of cell migration [122]. The luteolin also could synergize the antitumor effects of 5-fluorouracil on HepG2 and Bel7402 cells, which might be related with apoptosis and regulation of 5-fluorouracil metabolism [123]. Moreover, Chian et al [124] demonstrated *in vivo* that luteolin inhibited nuclear factor (erythroid-derived 2)-like 2 (Nrf2) in mouse liver and significantly enhanced the therapeutic effect of cisplatin both in animal and in cell lines. The luteolin was able to significantly inhibit cellular growth, cell migration, and induce S and G2/M cell cycle arrest and apoptotic cell death in glioblastoma multiforme (GBM 8401) cells [125], and to attenuate the growth of estrogen receptor in human breast cancer cells (MDA-MB-231) both *in vitro* and *in vivo* assays suppressing the proliferation of breast cancer cells in mouse model [126]. Additionally, Yang et al [127] combined luteolin and paclitaxel, which led to an enhancement of apoptosis in human breast cancer cells (MDA-MB-231) and to a decrease in orthotopic tumor growth in nude mice. Quercetin and kaempferol are the two most studied flavonols and were investigated in various human and murine cell lines by different authors, with effective results against cells of different carcinoma [128-134]. The effects of genistein, an isoflavonoid, in prostate carcinoma were assessed by using *in vitro* assays with human cell lines [135] and *in vivo* models using murine [136]. The results of these studies indicated that genistein was capable to inhibit cell proliferation as well as to upregulate glutathione peroxidase and downregulate apoptosis inhibitor agents. In stilbene group, resveratrol represent the most important PC. This compound presented a direct antitumor activity against many carcinoma types including leukemia, neuroblastoma, pancreatic, breast, prostate and renal carcinoma [137,138].

The hepatoprotective effects of same PC isolated from natural sources are presented in Table 5. Phenolic acids, namely caffeic, chlorogenic and gallic acids, showed hepatoprotective effects through different mechanisms [139-142]. Within flavanones group, hesperetin and naringenin emerge with hepatoprotective properties. The hesperetin is responsible for combating against CCL<sub>4</sub> (carbon tetrachloride)-induced hepatic damage in mice through decrease of various enzymes [143]. The naringenin showed hypoglycemic, vasorelaxant and hepatoprotective properties through decrease of the enzymes involved in liver diseases [144]. Regarding the flavone group, apigenin and luteolin play an important role in hepatoprotective effects. Various authors described this PC as displaying hepatic properties including the decrease of different enzymes harmful to the liver cells as well as ability to inhibit HepG2 cell line (liver carcinoma) [139,145,146]. Isorhamnetin, kaempferol, myricetin and quercetin are some examples of flavonols implicated in hepatoprotective effects. These compounds were able to reduce damaging enzymes such as aspartate transaminase (AST) and alanine transaminase (ALT) [142,143,147]. Additionally, Pereira et al [139] described kaempferol as hepatoprotective agent via reducing the growth of HepG2 cell line.

### **3.2. *In vitro* versus *in vivo* performance**

Several studies conducted *in vitro* were designed to evaluate the bioactivity of phenolic compounds extracted from different plants. Despite the scientific relevance of these studies, biochemical, physiological or metabolic parameters are not considered [2,3,148]. Thus, there has been an exponential increase in the number of *in vivo* studies using rats, mice and rabbits; however, studies involving humans are still very scarce [149]. Unfortunately, there is a large number of studies on the *in vitro* properties of different natural matrices that did not advance to *in vivo* studies. But, after metabolism, the various compounds can be converted to their active forms or otherwise inactivated or attached to biomolecules, which can modify its original purpose [148]. These effects are not considered on the *in vitro* assays and, therefore, *in vivo* validation is always required [3].

In spite of recent scientific advances, the bioavailability of PC is not clearly defined since, during ingestion, digestion and absorption these molecules can undergo various biochemical reactions [6, 150]. Therefore, the *in vivo* effect of PC cannot simply be extrapolated from the *in vitro* activities. For example, the antioxidant activity of a particular food verified *in vitro* differs when tested *in vivo* [151]. Otherwise, some phenolic complexes have low antioxidant activity when studied *in vitro*, but *in vivo* may undergo metabolic transformation into simpler compounds, which leads to an increase in plasma antioxidant capacity [152].

Reviewing Figure 3 it is possible to verify that although the *in vivo* and *in vitro* studies with PC have started in 1960, the highest impact has been observed since 1990 for *in vitro* studies, and five years later for *in vivo* assays. Despite the exponential increased number of studies, *in vitro* experiments are always higher than *in vivo* studies. In contrast there is a higher number of patents for *in vivo* than *in vitro* assays suggesting a growing interest from the industry towards these outputs.

### **3.3. Bioavailability of phenolic compounds as a main factor in bioactivity**

The large amounts of PC consumption through feed is not directly related to improved bioavailability profile [153]. The health benefits from natural PC depend on their absorption and metabolism [154].

*In vitro* evaluation systems to determine the bioactive potential of PC are based on the surface of organs such as the inner wall of the gastrointestinal tract, but such systems cannot reflect antioxidant *in vivo* effects [77] because the physico-chemical characteristics (molecular size, base structure, degree of polymerization and/or glycosylation, solubility, interaction with other compounds) are major factors limiting the PC action [153].

The bioavailability is considered a fundamental step to guarantee the bioefficacy of PC, i.e., at nutritional level, the bioavailability is the fraction of a given food that the organism can utilize, and is therefore a matter of nutritional efficacy [155]. So, the bioavailability of the PC can be affected by various factors that may interfere directly in bioavailability or decreasing the PC amounts in food. External factors, food processing, interaction with other compounds and intestinal factors are some examples of those factors [156]. The bioavailability depends on different and complex processes such as liberation, absorption, distribution, metabolism and elimination phases [155], however, the absorption at intestinal level is considered the limiting factor contributing to the bioavailability decrease. Permeability, lipophilicity, uptake and efflux by transporters are some factors that affect the amounts of each compound

which is absorbed by the mesenteric architecture and sent to the liver tissues through intestinal cells [157].

Phenolic compounds with small-molecular weight, for example, gallic acid and isoflavones are easily absorbed through the gastrointestinal tract [153]. On the contrary, the majority of PC are relatively poorly absorbed (absorption rates between 0.3 and 43%) and the circulation in plasma concentrations of their metabolites can be low [155]. For instance, in flavonols group, the quercetin and kaempferol demonstrated various biological *in vitro* effects [158]. Nevertheless, the use of these flavonols as a health promoting compound has been limited due its poor bioavailability caused by low water solubility, poorly absorption rate and high instability in neutral and alkaline media including different organs such as small intestine, colon, liver and kidney [157,159]. Additionally, in flavones group, the use of apigenin is also very limited because of its instability and poor solubility in the pure form [160].

## **4. PHENOLIC COMPOUNDS IN FUNCTIONAL FOODS AND NUTRACEUTICALS**

### **4.1. Health claims**

The health claims of food or its constituents are an essential tool when it comes to marketing, that is, consumers are more likely to consume foods when they are sold as “healthy food”. However, regulatory identities are necessary to avoid false claims and deception of consumers [161]. There is a large and growing number of studies conducted in order to characterize the bioactivities of different PC with the aim to introduce them in food and add value to foodstuffs. Despite all the interesting results previously mentioned, PC application in food industry has to overcome various laws and rules. In European Union, the utilization of health claims was regulated in 2006 by EFSA. The health claims suggest or imply the relationship between the food or its constituents with health [161].

The regulations of the European Commission are quite restrictive in their use and applicability. Despite the wide variety of PC with promising bioactivities, the only ones authorized with health claims in the Regulation (EU) No 432/2012 are phenolic olive oil. Still, the conditions of the use of this health claim are limited to a minimum concentration of hydroxytyrosol in a certain amount of olive oil (5 mg of hydroxytyrosol in 20 g of olive oil). In these conditions, it is possible to claim that olive oil PC contribute to the protection of blood lipids from oxidative stress [162].

### **4.2. Presence in foods with reported bioactivity**

PC are currently receiving high attention because of their beneficial health effects, mainly antioxidant [163,164], anti-inflammatory [165,166], antimicrobial [167], cardio-protective [168], cancer-preventive [16] and neuro-protective [169] properties. These compounds assume different forms in the body allowing prevention or treatment of these diseases [170-173]. Therefore, several studies indicate that an increase in the consumption of foods rich in PC can be associated with the prevention of the mentioned diseases [64,168,171,174].

Table 6 includes examples of some foods rich in PC with the respective reported biological effects associated to their antioxidant activity (prevention of cardiovascular disease and cancer).

The wine, particularly, red wine, is an important source of flavonoids, especially catechins and procyanidins that proved to have a significant protective effect against coronary heart disease (CHD) [175,176]. A correlation was also noticed between increasing levels of flavonoids ingestion from fruit and vegetables and the reduction in CHD [177,178]. Catechins and procyanidins have shown, *in vitro*, to be powerful inhibitors of LDL (Low Density Lipoprotein) oxidation, higher than, for example,  $\alpha$ -tocopherol [179]. Moreover, it was described that the moderate consumption of wine by humans leads to an increase in the antioxidant capacity of plasma [180]. Other studies have been carried out on the antioxidant activity – through inhibition of copper-catalysed oxidation of human LDL – of a selection of Californian wines. The relative inhibition of LDL oxidation (calculated with respect to the total phenol concentration of each sample) varied from 46% to 100% for red wines, and from 3% to 6% for white wines [181].

The quercetin, flavonol also presented in the wine, when ingested in large quantities reduces the incidence of lung cancer [182] and ischemic heart disease [176]. Teissedre & Landrault [175] studied the *in vivo* effect of gallic acid (originated from red wine) in rats, noticing a reducing mortality rate from CHD. Catechins present in green tea affect lipid metabolism by different pathways and prevent the appearance of atherosclerotic plaque. Its intake decreases the absorption of triglycerides and cholesterol and these findings are in accordance with the fact that it increases fat excretion [183]. Green tea, due to its components, is also appointed to assist in Alzheimer's disease prevention [184].

Sesso, Gaziano, Buring & Hennekens [185] studied the relationship between tea and coffee consumption and myocardial infarction; in this study it was verified a 44% reduction of the cardiovascular risk in the individuals drinking more than one cup of tea per day. For the coffee, significant correlation was achieved. All absorbed catechins, procyanidins and metabolites can contribute to increased antioxidant capacity of plasma. Their cardioprotective effects stem from the ability to inhibit lipid peroxidation, chelate redox-active metals and attenuate other processes involving ROS [176].

The major dietary sources of stilbenes include grapes, wine, soy, peanuts, and peanut products [186]. Stilbenes, namely resveratrol, have shown effects in preventing or treating certain diseases such as breast cancer [187,188] and skin tumors [189]. The resveratrol has been shown to inhibit ribonucleotide reductase and other cellular events associated with initiation, promotion and progression of carcinogenesis [189]. The orange juice and grapefruit juice contain high amounts of hesperetin and naringenin and exhibit anti-carcinogenic effects [190]. Tan et al [129] also studied the antiangiogenic potential of quercetin, which demonstrated to inhibited several important steps of angiogenesis including proliferation, migration and tube formation of human microvascular dermal endothelial cells. Another study reported the synergistic effect of grape components in the prevention of diabetes and cardiovascular diseases, and in the promotion of oral health [184].

The biological activities of PC in the human body are mostly attributed to the ability of these compounds to exert antioxidant actions. The main antioxidant activity of the polyphenols consist in potentiate cell detoxification systems, such as the superoxide dismutase, catalase or glutathione peroxidase systems, and inhibit ROS generating enzymes, such as xanthine oxidase and NADPH oxidase (Nicotinamide Adenine Dinucleotide Phosphate-Oxidase) [168]. However, recent studies suggest that the mechanisms by which PC exert their protective action against cardiovascular diseases and cancer, are not simply due to their redox properties, but due to the ability to bind directly to proteins [191]. Such a mode

of action would induce the inhibition of key enzymes, the modulation of cell receptors or transcription factors, as well as the perturbation of protein aggregates, which can regulate cell functions related to, e.g. growth and proliferation, inflammation, apoptosis, angiogenesis, metastasis, and immune responses, in various ways by affecting signal transduction pathways [168,192-194]. However, there is a great diversity of PC, and the way in which they interact with the proteins depends on the physical chemical properties of both [191].

Summarizing, PC can be considered as good candidates for the prevention and treatment of several diseases. Ongoing studies are particularly devoted to understand all action mechanisms in the body, including bioavailability features.

#### **4.3. Applications in functional foods and nutraceutical formulations**

Nowadays, some functional foods and nutraceuticals capturing consumer's interest can be found commercially. The scientific community was able to prove the health beneficial effects of this type of products, which the food and pharmaceutical industries have emulated, making viable the production of some novel and original products of high income. The medicinal and aromatic plants play an important role in this area due to their antioxidant, antimicrobial and other beneficial effects in combating certain diseases.

Figure 4 schematizes possible PC intake processes through fortified foods and their effects in the human body. The incorporation of these compounds in food can be performed directly in its free form; however, microencapsulation technique emerged as a very effective and promising strategy to assure bioavailability of these compounds, helping to surpass problems of food processing and ingestion [195]. After ingestion the compounds are absorbed into the bloodstream causing changes in various cellular mechanisms, leading to prevention of various diseases.

There are many articles in the literature that demonstrate the bioactivity of various plants and fruits PC's, studies reporting its application in functional foods or nutraceutical formulations development, is still scarce. Table 7 lists some examples of PC used as nutraceuticals or bioactive compounds in functional foods. Isoflavones of soy were used in dietary supplements to control the menopausal symptoms, while anthocyanins of cranberry were used in nutraceutical capsules for antioxidant purposes. Moreover examples of case studies with incorporation of phenolic extracts into food matrices are also provided in Table 7. Phenolic extracts of pomegranate fruits were incorporated by Robert et al [196] and Pillai et al [197] in yogurt and pasta, respectively, to enhance antioxidant activity. The phenolic extracts of pomegranate were also incorporated by Çam et al [198] into ice cream aiming at enhancing the antioxidant and  $\alpha$ -glucosidase inhibitory activities. Ezhilarasai et al [199] and Pasrija et al [200] incorporated garcinia and green tea phenolic extracts, respectively, in bread resulting in a new product with increased antioxidant activity. Chouchouli et al [201] and Martins et al [202] used grape seed and blackberry flowers, respectively, to add value and antioxidant activity to functional yogurts. The incorporation of *Veronica* phenolic extracts caused an increase in the antibacterial activity of a new cream cheese [203]. More recently, Caleja et al [54,55], incorporated phenolic extracts in cottage cheese using fennel and chamomile extracts, reporting a higher antioxidant activity and an extending shelf-life in comparison with the control cottage cheese without extracts. Also in cottage cheese, the same research

group incorporated mushroom [204] and rosemary extracts [205] to improve antioxidant properties. Fennel and chamomile extracts were also incorporated in yogurts and showed best results when compared with control and yogurts with a synthetic additive (potassium sorbate – E202) [206]. Another recent study described the incorporation of PC of guava flower in bread melanoidins, which retained its quality while adding antioxidant value [207]. Finnaly, Miceli et al [208] showed that the incorporation of borage in fresh pasta introduced antimicrobial properties.

#### 4.4. Present market and future tendency

The Compal company (Sumol+Compal, S.A.) has developed products defined as functional and marketed in the form of nectar, as is the case of Compal Vital AntiOx<sup>®</sup>, ensuring antioxidant properties due to the presence of a selected range of red fruits (<http://www.compal.pt/#/pomar/nectares/vital/>). Guimarães et al [209] proved that the red fruits are rich in phenolics providing antioxidant activity. However, when added to food, the PC are not present in its pure form, they are added mainly as rich extracts or fruits pulps.

In the field of nutraceuticals and dietary supplements, it is also observed a growing interest enforced by the increase of published works on the topic. In literature, it is common to find the description of product formulations incorporating PC, but through the use of natural extracts typically used to fortify foods. These products have been commonly launched on the market, in the form of tablets or syrups, claiming health benefits due to the presence of PC [210].

Magiera et al [211] reported the presence of fourteen flavonoids in a dietary supplement (not specified), relating them with the shown antioxidant capacity. In another study, performed by Pereira et al. [212], the phenolic profile of different formulations of dietary supplements (infusions, syrups and tablets) based on *Cochlospermum angolensis* Welw, also known as borututu, used for the treatment and prevention of liver diseases, was described. The amount of PC was also related with the observed antimicrobial activity of the supplements. A similar study was conducted by Bresciani et al [213] in which the authors performed the phenolic characterization of three herbal supplements, through identification by MSn-UHPLC.

Even the development of functional foods and nutraceuticals is considered a fast process, these products often require sound scientific evidence before being introduced in the market. Clinical studies are generally very expensive and thus not affordable for most of the companies dealing with the manufacture this type of food products, which cannot bear the expenses to carry out all tests [51,184,214]. For each clinical study, research companies and/or universities need to combine hundreds to thousands of subjects. On average each of these studies can cost several thousands of dollars [41].

Despite the fact that laws related to this type of products are quite different among countries, the labeling rules are similar. It is through labeling that consumers have access to all information concerning food composition and respective health benefits, which in the case of functional foods and nutraceuticals becomes very important [184]. Some studies indicate that women are more influenced to buy new products [215], partly because they are more concerned with health issues [39] but also since they are generally in charge of home shopping.

The main factors influencing functional foods purchasing are: lifestyle, health awareness, taste for healthier foods [216] and packaging design. So, it is important that consumers have knowledge and familiarity with functional foods [39], product safety [39,217] and information concerning the base product (food matrix) [39,218]. Moreover, legislation changes in the EU panorama in what concerns new products has also helped consumer attitude modification. In that context a greater reliance on the information passed by the labels and advertising regarding nutritional and health virtues of these food products is evident [39].

In general, the functional products still need to overcome some obstacles to ensure success in the market and win consumer confidence. Therefore, to support the high demand for functional foods it is necessary to combine efforts of various areas such as science, industry, market, media, education and governmental policies, and thus manage to develop a reputable product image. The product promotion should be perceived by all age groups, from the youngest to the elderly, and thus must be carried out simply and clearly with accessible vocabulary [184,219]. However, the success the functional foods also depends on the organoleptic attributes, especially flavor, appearance, price and health claims [31]. Therefore, the food industry has to take into consideration some factors for the development/restructuring of functional foods, highlighting: sensory acceptance, price, stability, chemical and functional properties [41,220].

Technological development also allows greater innovation in food products. According with Betoret et al [41], the technologies applied to foods can be divided into three groups. The first group is formed by traditional technologies in food processing. The second group encompasses techniques used to protect biologically active compounds, such as microencapsulation, and the development of edible films, coatings and vacuum impregnation. The third group is made up of the latest technologies that can be applied to develop customized functional products.

PC derived from natural sources are known to exhibit various bioactivities [168], and thus their introduction into food matrices will provide a higher intake. However, the PC can exhibit several instabilities when introduced in foods, arising either from food processing (manufacturing temperatures) or long storage periods in contact with the food matrix, among other factors [41,195]. Thus, technologies progress has introduced advances in the food industry, enabling innovation into food products development. In this context, microencapsulation is one of most frequently applied methods to overcome problems related to PC instability and assure controlled release in foods [221,222].

Microencapsulation is emerging as a technique capable of protecting bioactive compounds, such as phenolics, by means of a protective material (e.g. natural polymer or waxes). Some authors state that with this technique it is possible to protect compounds from adverse conditions such as light, oxidation, hydrolysis and moisture contact, thereby ensuring functionality maintenance and thus bioavailability [195,223-225]. When the bioactive is added to the food matrix in the form of microparticles it is possible to minimize problems related to food storage time (reduce compounds degradation) and prevent deleterious interactions with the food matrix [41,202]. However, it is desired that the introduced microparticles do not alter food texture and flavor [41].

## 5. CONCLUSIONS



Throughout of this review, the biological effects of polyphenols, their action when incorporated into a foodstuff or nutraceutical formulation, as well as their relevance to human health were evidenced. It was shown how PC consumption provides significant protection against disease development and progression, including in cardiovascular and cancer diseases. Despite the existing literature evidences reporting that polyphenols represent a great hope in the prevention of many chronic human diseases, there are still in our opinion fields to explore, particularly in what concerns the elucidation of some action mechanisms. The demand for functional foods in EU varies considerably from country to country due mainly to tradition and cultural heritages. In terms of marketing, functional foods must be promoted in a clear and objective manner so they can be easily recognized by final consumers. The market should promote clearly the product avoiding excessive scientific vocabulary. The labels should contain a specific logo for these foods ensuring an easy recognition and differentiation from other products.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**Table 1. Examples of phenolic compounds with antioxidant activity.**

Phenolic compound		Effect	Type of assay	Reference
Phenolic acids	Gallic acid	Increase of P-Form PST activity	<i>In vivo</i> (rats)	[75]
Anthocyanins	Cyanidin; Delphinidin; Malvidin; Petunidin	Donation of electrons or hydrogen atoms from hydroxyl moieties to free radicals	<i>In vivo</i> (rats)	[76]
Flavan-3-ols	Catechin	DPPH radical scavenging activity and linoleic acid peroxidation inhibition	<i>In vitro</i> (rats)	[77]
		Superoxide radical scavenging activity and reducing power	<i>In vitro</i>	[78]
Flavones	Apigenin	Reduction of intracellular reactive oxygen species	<i>In vitro</i>	[79]
		DPPH radical, superoxide radical and hydroxyl radical scavenging activity	<i>In vitro</i> (mice)	[80]
	Kaempferol	Stimulation of antioxidant enzymes to provide additional protection for heart, liver and kidney.		
		DPPH radical scavenging activity, reducing power and lipid peroxidation inhibition	<i>In vitro</i>	[81]

DPPH - 2,2-diphenyl-1-picrylhydrazyl; PST – phase II hepatic phenol sulfotransferases



**Table 2. Examples of phenolic compounds with antimicrobial activity.**

Phenolic compound		Bacteria/Fungi	Type of assay	Reference
Phenolic acids	Chlorogenic acid	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i> , <i>Candida albicans</i> , and <i>tropicalis</i> (antiwound infection, repair and contraction)	<i>In vitro</i> <i>In vivo</i> (rodent)	[82]
	Ferulic acid	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , and <i>Listeria monocytogenes</i>	<i>In vitro</i>	[83]
	Gallic acid	<i>Escherichia coli</i> , <i>Salmonella typhi</i> , <i>Vibrio cholera</i> , <i>Enterococcus faecalis</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> ; <i>Microsporium gypseum</i> , <i>Trichophyton rubrum</i>	<i>In vitro</i>	[84]
		<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , and <i>Listeria monocytogenes</i>	<i>In vitro</i>	[83]
		<i>Campylobacter coli</i> , <i>Campylobacter jejuni</i>	<i>In vitro</i>	[84]
		<i>Helicobacter pylori</i>	<i>In vitro</i>	[85]
		<i>Escherichia coli</i>	<i>In vitro</i>	[86]
Flavan-3-ols	Catechin	<i>Candida albicans</i>	<i>In vitro</i>	[88]
		<i>Helicobacter pylori</i>	<i>In vitro</i>	[86]
		<i>Escherichia coli</i>	<i>In vitro</i>	[87]
Flavanones	Hesperitin	<i>Staphylococcus aureus</i> ; <i>Candida albicans</i>	<i>In vitro</i>	[89]
	Naringenin	<i>Lactococcus lactis</i>	<i>In vitro</i>	[90]
		<i>Staphylococcus aureus</i>	<i>In vitro</i> <i>In vivo</i> (mice)	[91]
Flavones	Apigenin	<i>Pseudomonas aeruginosa</i> , <i>Salmonella typhimurium</i> , <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i> and <i>Enterobacter aerogenes</i>	<i>In vitro</i>	[92]
		<i>Staphylococcus epidermis</i> , <i>Bacillus subtili</i> , <i>Saccharomyces cerevisiae</i>	<i>In vitro</i>	[93]
	Luteolin	<i>Staphylococcus epidermis</i> , <i>Bacillus subtili</i> , <i>Saccharomyces cerevisiae</i>	<i>In vitro</i>	[93]
Flavonols	Keampferol	<i>Enterococcus faecalis</i>	<i>In vitro</i>	[94]
	Rutin	<i>Acinetobacter baumannii</i> , <i>Staphylococcus aureus</i> , <i>Enterococcus faecalis</i> , <i>Bacillus subtilis</i> .	<i>In vitro</i>	[95]
Isoflavones	Genistein	<i>Vibrio harveyi</i>	<i>In vitro</i>	[96]
		<i>Bacillus anthracis</i>	<i>In vitro</i>	[97]
		<i>Klebsiella pneumonia</i> , <i>Salmonella typhi</i>	<i>In vitro</i>	[98]
Stilbenes	Resveratrol	<i>Enterococcus faecalis</i>	<i>In vitro</i>	[94]
		<i>Candida albican</i>	<i>In vitro</i>	[102]
		<i>Campylobacter spp</i> , <i>Arcobacter butzleri</i>	<i>In vitro</i>	[99]
		<i>Saccharomyces. cerevisiae</i> ; <i>Aspergillus ninger</i> , <i>Penicillum. expansum</i>	<i>In vitro</i>	[100]
		<i>Helicobacter pylori</i>	<i>In vitro</i>	[101]

**Table 3. Examples of phenolic compounds with anti-inflammatory activity.**

Phenolic compound		Effect	Type of assay	Reference
Flavanone	Hesperetin	Inhibition of tumor necrosis factor $\alpha$ and interleukin-6 in mouse macrophages	<i>In vitro</i>	[103]
Flavones	Apigenin	Inhibition of NF- $\kappa$ B transcriptional activation	<i>In vivo</i> (mice)	[104]
	Luteolin	Inhibition of TNF- $\alpha$	<i>In vivo</i> (mice)	[105]
		Inhibition of NF- $\kappa$ B transcriptional activation	<i>In vivo</i> (mice)	[104]
		Reduction of nitric oxide synthase expression	<i>In vitro</i>	[106]
		Downregulation of TLR4, TLR5, NF- $\kappa$ B, p-p38MAPK	<i>In vivo</i> (rats)	[107]
		Prevention of the activity of Hsp90	<i>In vitro</i> <i>In vivo</i> (mice)	[108]

NF-  $\kappa$ B – factor nuclear kappa B; TNF- $\alpha$  - tumor necrosis factor  $\alpha$ ; TLR4 – toll-like receptor 4; TLR5 - toll-like receptor 5; p-p38MAPK – phosphor-p38 MAPK; Hsp90 – heat shock protein 90.

**Table 4. Examples of phenolic compounds with antitumoral effects.**

Phenolic compound	Type of tumor	Type of assay	Reference
Phenolic acids	Gallic acid	Leukemia	<i>In vitro</i> (human cell lines) [109]
		Glioma	<i>In vitro</i> (human cell lines) [110]
		Lung carcinoma	<i>In vitro</i> (murine cell lines)
			<i>In vitro</i> (human cell lines) [111]
Anthocyanins	Cyanidin	Colorectal carcinoma	<i>In vitro</i> (human cell lines) [112]
	Delphinidin	Prostate carcinoma	<i>In vitro</i> (human cell lines) [113]
		Colorectal carcinoma	<i>In vitro</i> (murine cell lines)
			<i>In vitro</i> (human cell lines) [112]
Flavan-3-ols	Catechin	Breast cancer (MCF-7)	<i>In vitro</i> (human cell lines) [115]
		Melanoma	<i>In vitro</i> (human cell lines) [114]
			<i>In vitro</i> (murine cell lines)
Flavanones	Hesperitin	Breast carcinoma	<i>In vitro</i> (human cell lines) [116]
		Cervical carcinoma	<i>In vitro</i> (human cell lines) [117]
	Naringenin	Skin carcinoma	<i>In vitro</i> (human cell lines) [118]
Flavones	Apigenin	Lymphoma	<i>In vitro</i> (human cell lines) [119]
		Pancreatic cancer	<i>In vitro</i> (human cell lines) [120]
	Luteolin	Colon carcinoma	<i>In vitro</i> (human cell lines) [121]
		Non-small cell lung cancer	<i>In vitro</i> (human cell lines) [122]
		Hepatocellular carcinoma (HepG2 and Bel7402)	<i>In vitro</i> (human cell lines) [123]
		Non-small cell lung cancer	<i>In vivo</i> (mouse cell lines) [124]
		Breast cancer (MDA-MB-231)	<i>In vitro</i> (human cell lines) [127]
		Glioblastoma (GBM 8401)	<i>In vitro</i> (human cell lines) [125]
		Breast cancer (MDA-MB-231)	<i>In vitro</i> (human cell lines) [126]
		Breast cancer (MDA-MB-231)	<i>In vitro</i> (mouse cell lines)
			<i>In vitro</i> (human cell lines)
Flavonols	Kaempferol	Hepatocarcinoma	<i>In vitro</i> (human cell lines) [131,132]
		Pancreatic carcinoma	
		Breast cancer (MCF-7)	<i>In vitro</i> (human cell lines) [134]
			<i>In vivo</i> (female mice)
	Quercetin	Ovarian cancer	<i>In vitro</i> (human cell lines) [133]
		Gastric adenocarcinoma	<i>In vitro</i> (human cell lines) [128-130]
		Hepatocellular carcinoma	
Isoflavones	Genistein	Leukemia	
		Neuroblastoma	
Stilbenes	Resveratrol	Pancreatic carcinoma	
		Breast carcinoma	
		Prostate carcinoma	
		Renal carcinoma	

**Table 5. Examples of phenolic compounds with hepatoprotective effects.**

Phenolic compound	Effect	Type of assay	Reference
Phenolic acids	Caffeic acid	GI <sub>50</sub> = 52.06 µg/mL	<i>In vitro</i> (HepG2 cells) [139]
	Chlorogenic acid	↓ HBV DNA replication	<i>In vitro</i> [141]
	Gallic acid	↓AST, ↓ALT, ↓TB, ↓GGT ↑SOD, ↑CAT, ↑GSH, ↑lipase, ↑α-amylase, ↑Alb, ↓ALP, ↓AST, ↓ALT, ↓triacylglycerol, ↓TB, ↓glucose, ↓cholesterol	<i>In vivo</i> (rats) [142] <i>In vivo</i> (rats) [140]
Flavanones	Hesperitin	↓AST, ↓ALT, ↓MDA, ↑SOD, ↑GSH-Px	<i>In vivo</i> (mice) [143]
	Narigenin	↓PGT, ↓ALP, ↑γ-GTP	<i>In vivo</i> (rats) [144]
Flavones	Apigenin	↓SGOT, ↓SGPT, ↓ALP, ↓TG, ↓TC, ↓LDL, ↓BUN, ↓creatinine, ↓TB, ↑HDL	<i>In vivo</i> (wistar rats) [146]
		GI <sub>50</sub> = 52.06 µg/mL	<i>In vitro</i> (HepG2 cells) [139]
	Luteolin	↓SGOT, ↓SGPT, ↓ALP, ↓TG, ↓TC, ↓LDL, ↓BUN, ↓creatinine, ↓TB, ↑HDL	<i>In vivo</i> (wistar rats) [146]
		GI <sub>50</sub> = 85.8 and 20.2 µM	<i>In vitro</i> (Hep G2 cells) [145]
Flavonols	Isorhamnetin	↓AST, ↓ALT, ↓TB, ↓GGT	<i>In vivo</i> (rats) [142]
	Kaempferol	↓AST, ↓ALT, ↓TB, ↓GGT	<i>In vivo</i> (rats) [142]
		GI <sub>50</sub> = 52.06 µg/mL	<i>In vitro</i> (HepG2 cells) [139]
	Myricetin	↓AST, ↓ALT, ↓TB, ↓GGT	<i>In vivo</i> (rats) [142]
	Quercetin	↓AST, ↓ALT, ↓MDA, ↑SOD, ↑GSH-Px	<i>In vivo</i> (mice) [143]
		↓AST, ↓ALT, ↓TB, ↓GGT	<i>In vivo</i> (rats) [142]
	Rutin	↓ALP, ↓ALT, ↓AST	<i>In vivo</i> (wistar rats) [147]

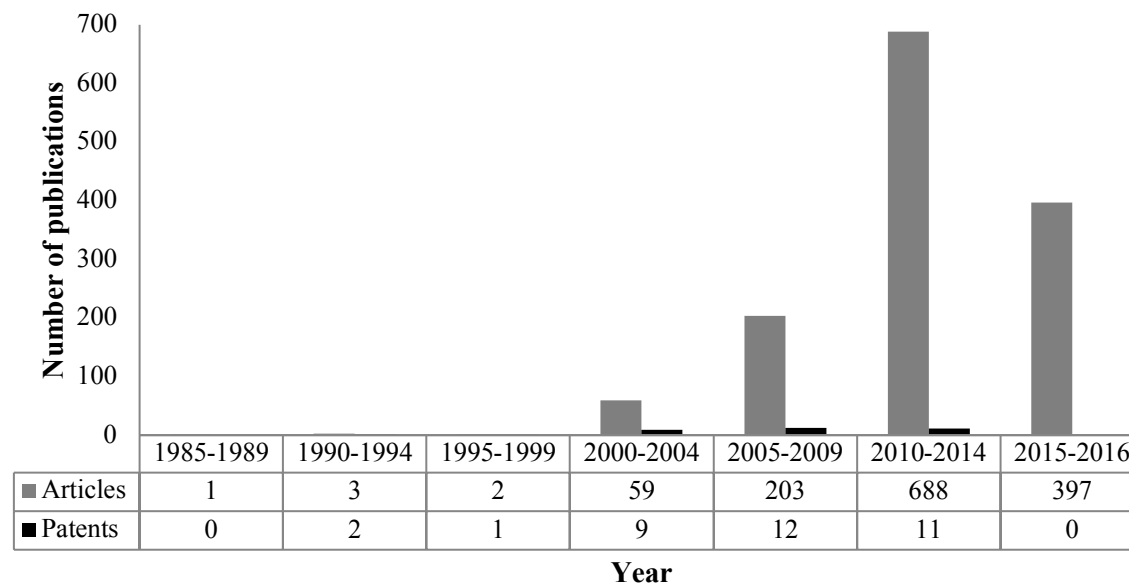
Alb – Albumin; ALP – alkaline phosphatase; ALT – Alanine transaminase; AST – Aspartate transaminase; BUN – Blood urea nitrogen; CAT – Catalase; DNA - deoxyribonucleic acid; GI<sub>50</sub>- Sample concentration that inhibited 50% of the net cell growth; GGT - γ-glutamyltransferase; GSH – reduced glutathione; GSH-Px – Glutathione peroxidase; HBV – Hepatitis B; HDL – High-density lipoprotein; HepG2 – hepatocellular carcinoma line; LDL – Low-density lipoprotein; MDA – Malondialdehyde; PGT – Glutamic-pyruvic transaminase; SGPT - Serum glutamate pyruvate transaminase; SOD – Superoxide dismutase; SGOT – Serum glutamate oxaloacetate transaminase; TB – Total bilirubin; TC – Total cholesterol; TG – triglyceride; γ-GTP – γ-glutamyl transpeptidase.

**Table 6. Phenolic compounds from food sources with reported biological effects mainly related with antioxidant capacity and prevention of cardiovascular disease and cancer.**

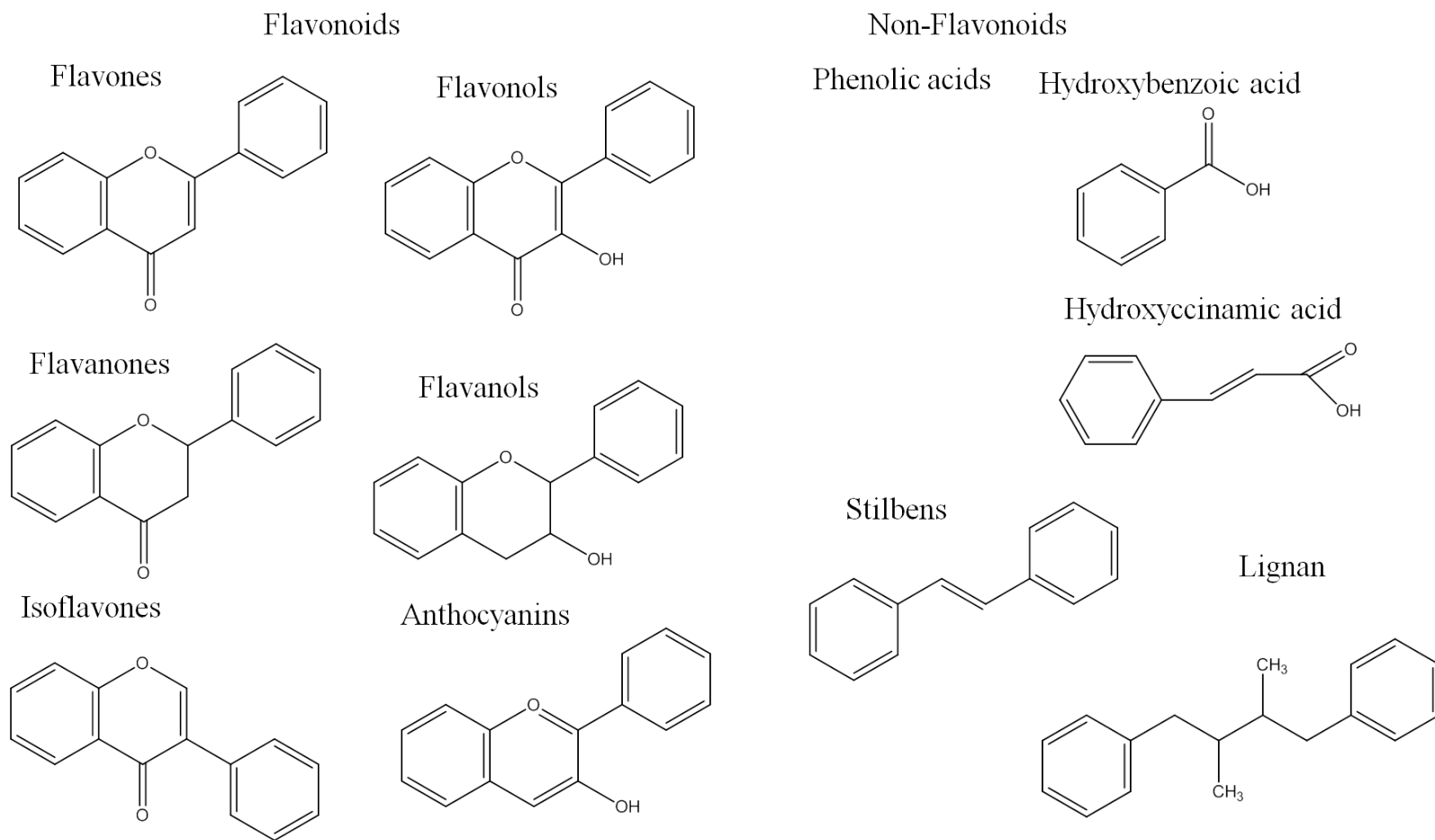
<b>Phenolic compound</b>		<b>Source</b>	<b>Reference</b>
Phenolic acids	Gallic acid	Red wine	[175]
Anthocyanins	Cyanidin Pelargonidin Peonidin Delphinidin Malvidin	Blackberry, blueberry, black grape, cherry, strawberry, red wine, plum	[226,227]
Condensed tannins	Procyanidin	Red wine, chocolate, cranberry juice and apples	[228]
Flavan-3-ols	Catechin	Fruits, vegetables, chocolate, lentil, green and black tea, wine, grapes and ginkgo	[184,229-234]
Flavanones	Hesperitin Naringenin	Orange, grapefruit and lemon juices	[190,192]
Flavones	Apigenin Luteolin	Parsley, celery, capsicum pepper and grape	[184,192]
Flavonols	Quercetin Kaempferol	Fruits, vegetables, and beverages such as tea and red wine	[184,235-237] [177,178,238,239]
Isoflavones	Genistein	Soy	[240,241]
Stilbenes	Resveratrol	Legumes, grapes, red wine, soy, peanuts and peanut products	[187,189,242-245]

**Table 7. Phenolic compounds used as nutraceuticals or bioactive compounds in functional foods.**

<b>Phenolic compound</b>	<b>Source</b>	<b>Application</b>	<b>Bioactivity</b>	<b>Reference</b>
Phenolic acids	Commercial	Infant cereals	Antioxidant properties and aroma	[246]
Anthocyanins	Cranberry ( <i>Vaccinium macrocarpon</i> Ait.)	Nutraceutical capsules	Antioxidant activity	[247]
Isoflavones	Soy ( <i>Glycine max</i> L.)	Dietary supplements	Antimenopausal symptoms	[248]
Phenolic extracts	Blackberry ( <i>Rubus ulmifolius</i> Schott) flowers	Yogurt	Antioxidant and antimicrobial activity	[202]
	Borage ( <i>Borago officinalis</i> L.)	Fresh Pasta	Antimicrobial activity	[208]
	Chamomile ( <i>Matricaria recutita</i> L.) flowers	Cottage chesse and yogurt	Antioxidant and antimicrobial activity	[54,206]
	Fennel ( <i>Foeniculum vulgare</i> Mill.) aerial parts	Cottage chesse and yogurt	Antioxidant and antimicrobial activity	[55,206]
	Garcinia ( <i>Garcinia cowa</i> Roxb) fruits	Bread	Antioxidant activity	[199]
	Grape seed ( <i>Vitis vinifera</i> L.)	Yogurt	Antioxidant activity	[201]
	Green tea ( <i>Cammelia sinensis</i> L.)	Bread	Antioxidant activity	[200]
	Guava ( <i>Psidium guajava</i> ) flower	Bread melanoidins	Antioxidant activity	[207]
	Pomegranate ( <i>Punica granatum</i> L.) fruits	Yogurt and pasta	Antioxidant activity	[196,197]
	Pomegranate ( <i>Punica granatum</i> L.) peels	Ice cream	Antioxidant and aglucosidase inhibitory activities	[198]
	Residues from brewing industry	Meat	Antioxidant and antimicrobial activity	[249]
	Rosemary ( <i>Rosmarinus officinalis</i> L.)	Cottage cheese	Antioxidant activity	[205]
	<i>Suillus luteus</i> (L.: Fries) Gray and <i>Coprinopsis atramentaria</i> (Bull.)	Cottage chesse	Antioxidant activity	[204]
	Redhead, Vilgalys & Moncalvo			
	Veronicas ( <i>Veronica montana</i> L.)	Cream cheese	Antibacterial activity	[203]

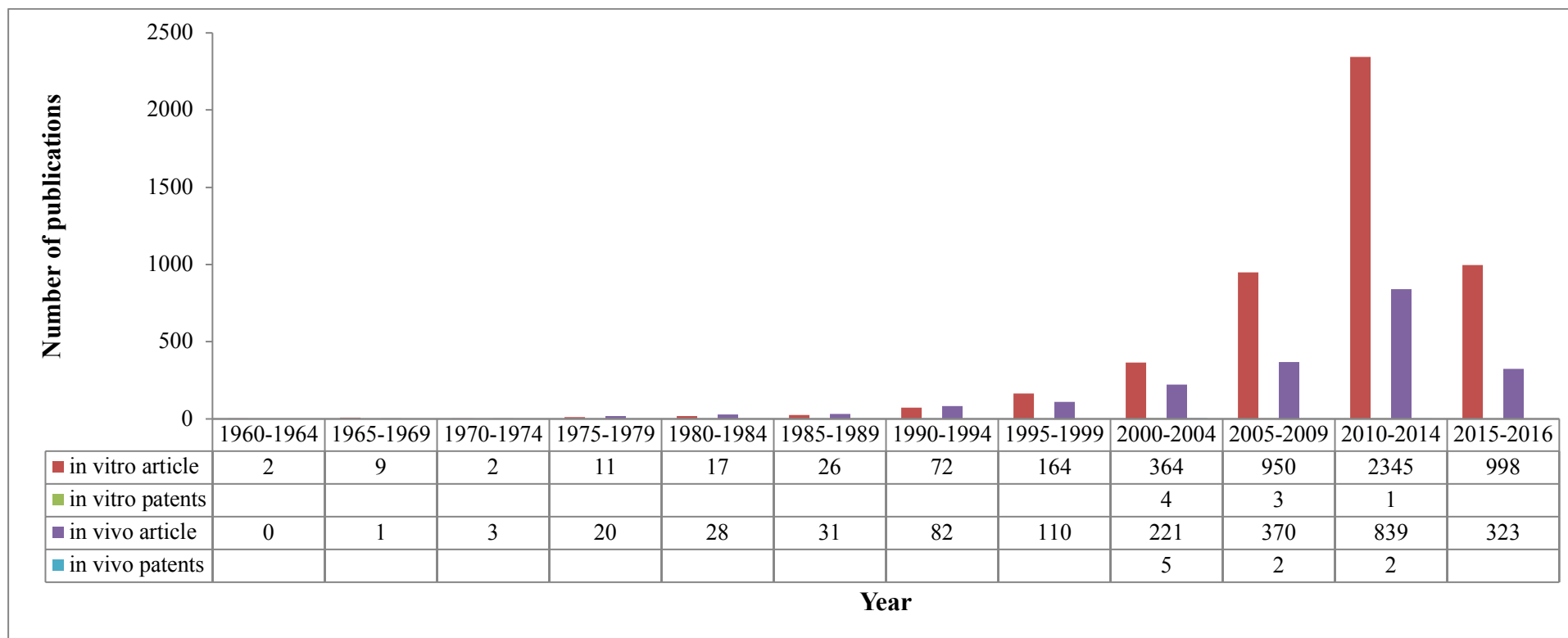


**Figure 1.** Number of research articles and reviews, and patents published in the period from 1985 to 2016 regarding functional foods and phenolic compounds (obtained on web of science, July 2016; keyword: functional food and phenolic compounds).

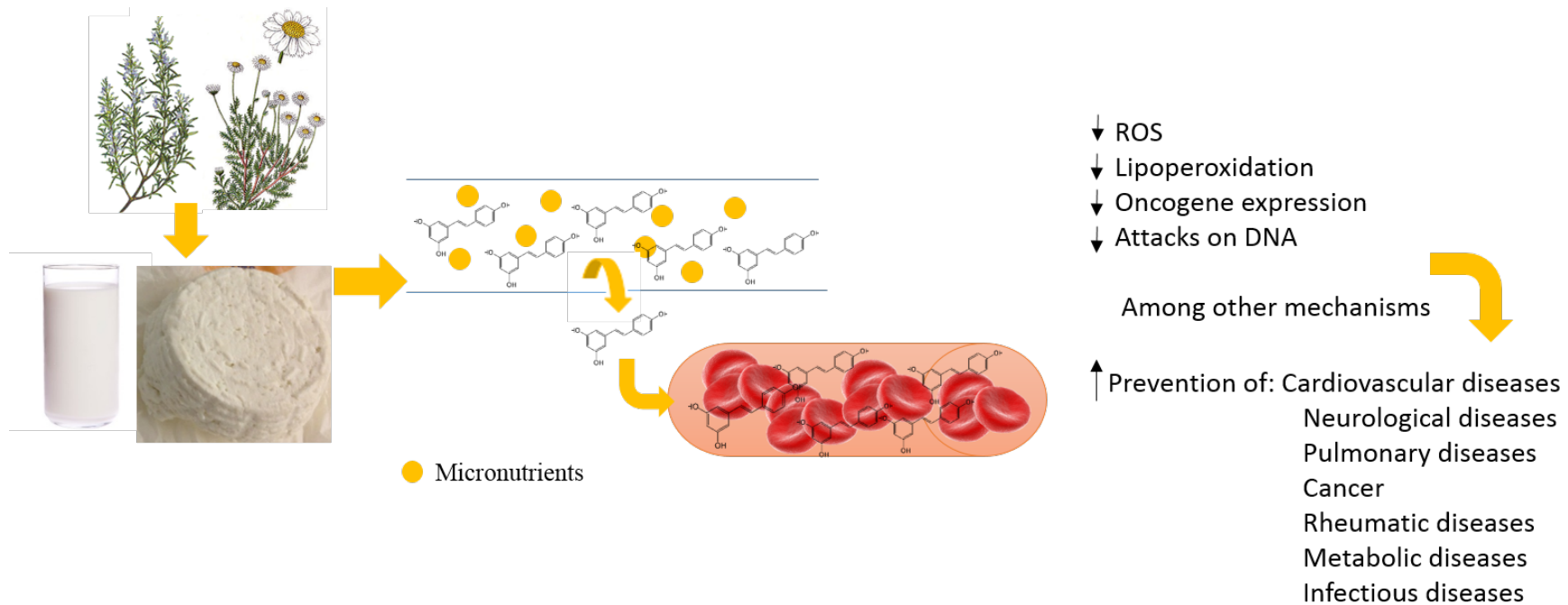


**Figure 2.** Chemical structure of subclasses of the flavonoids and non-flavonoids.





**Figure 3.** Number of research articles and reviews, and patents published in the period from 1985 to 2015 regarding phenolic compounds and *in vitro* or *in vivo* assays (obtained on web of science, July 2016; keyword: phenolic compounds and *in vitro*; phenolic compounds and *in vivo*).



**Figure 4.** Beneficial effects of phenolic compounds.