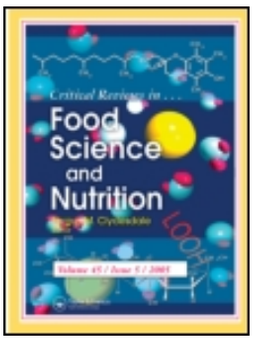

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# The Healthy Effects of Strawberry Polyphenols: Which Strategy behind Antioxidant Capacity?

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*Current evidence indicates that the consumption of strawberries, a natural source of a wide range of nutritive and bioactive compounds, is associated with the prevention and improvement of chronic-degenerative diseases. Studies involving cells and animals provide evidence on the anti-inflammatory, anticarcinogenic and antiproliferative activity of the strawberry. Epidemiological and clinical studies demonstrate that its acute consumption increases plasma antioxidant capacity, improves circulating inflammatory markers and ameliorates postprandial glycemic response. At the same time, a protracted intake reduces chronic inflammation and improves plasma lipid profile, supporting cardiovascular health, especially in individuals with increased risk for metabolic syndrome. To explain these beneficial effects, much attention has been paid in the past to the antioxidant properties of strawberry polyphenols. However, recent research has shown that their biological and functional activities are related not only to the antioxidant capacity but also to the modulation of many cellular pathways involved in metabolism, survival, proliferation, and antioxidant defenses. The aim of this review is to update and discuss the molecular and cellular mechanisms proposed in recent studies to elucidate the healthy effects of strawberry polyphenols against the most common chronic diseases, such as cancer, cardiovascular diseases, metabolic syndrome, and inflammation.*

**Keywords** Strawberry, polyphenols, inflammation, metabolism, cardiovascular diseases, cancer

## *INTRODUCTION*

Strawberries are a rich sources of nutritive compounds including minerals, vitamins, fatty acids, fibers, and secondary metabolites, as polyphenols, which are the most diffused and interesting bioactive compounds present in this fruit (Giampieri et al., 2012a). The main class of strawberry polyphenols are flavonoids, followed by ellagitannins, flavonols, flavanols, and phenolic acids: all these compounds show huge biological potentialities in humans, from antioxidant capacity to anti-inflammatory, antihypertensive, and antiproliferative abilities (Hakkinen et al., 2000; Hannnu, 2004; Giampieri et al., 2012a, Giampieri et al., 2014; Giampieri et al., 2015a; Mazzoni et al., 2015). In the last few years, a large number of studies have indeed evidenced a wide range of biological properties and potential benefits of strawberries, strawberry fractions, and even strawberry purified polyphenols in the

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prevention of the most widely known chronic diseases (Calder et al., 2011; Balansky et al., 2012; Romandini et al., 2013; Tulipani 2009a; Tulipani et al., 2014; Alvarez-Suarez et al., 2014; Alarcon et al., 2015; Azevedo et al., 2015).

The aim of the present work is to summarize recent evidence, obtained from *in vitro* and *in vivo* studies, on the potential of strawberries in the prevention and management of the most common pathologies, with particular attention to cellular and molecular mechanisms involved in the effects on human health.

### *Strawberry and Antioxidant Capacity*

In the past few years, antioxidant capacity has been considered as an indicator of foodstuff healthfulness and, therefore, much attention has been paid to the antioxidant properties of polyphenols: indeed the capacity of these compounds to scavenge free radicals and/or limit their formation has been accepted as the main mechanism through which they could counteract oxidative stress, preventing the onset and development of degenerative diseases. In this context, several *in vitro* investigations have been performed to outline the antioxidant activity of these compounds in different experimental models. Since skin is one of the main human tissues constantly exposed to a variety of environmental, chemical, and genotoxic agents, the protective effects of different strawberry polyphenols in skin well-being have been deeply analyzed. In human dermal fibroblasts stressed with different types of oxidant agents (i.e., $H_2O_2$, AAPH, and UV radiation) strawberry antioxidant capacity is essential for the prevention and/or reduction of free radical-induced skin damage, leading to the increase in viability, decrease in ROS concentration, lipid peroxidation, and DNA damage and improvement of mitochondrial functionality (Kaneko et al., 2003; Solomon et al., 2010; Giampieri et al., 2012b; Giampieri et al., 2014a; Giampieri et al., 2014b; Oyewole et al., 2014; Forbes-Hernández et al., 2014) (Fig. 1).

Besides skin, liver is another tissue frequently exposed to oxidative stress. Many *in vitro* studies highlight the polyphenol ability in counteracting oxidative stress in HepG2 cells, a common cellular model used to study liver, by increasing cell viability, decreasing ROS generation, markers of lipid peroxidation, DNA damage, and stimulating antioxidant enzymes (Kanazawa et al., 2006; Sarriá et al., 2012; Kim et al., 2011a; Kim et al., 2013a; Lee et al., 2014). Preliminary results recently obtained in our lab confirm the protective effects of polyphenols against oxidative stress: in fact, the treatment of AAPH-stressed HepG2 cells with strawberry extract is able to attenuate apoptosis, intracellular ROS levels, protein, lipid, DNA oxidation, and stimulate antioxidant enzymes and mitochondrial biogenesis (Fig. 1).

However, *in vitro* studies are often performed at experimental conditions not always comparable with the *in vivo* situation. Thus, it would be necessary to confirm the potential health-promoting effects of strawberries in animal and in human studies. Taking into account these critical points, in recent years several studies have been carried out *in vivo*, demonstrating the protective effects of polyphenols against oxidative stress,

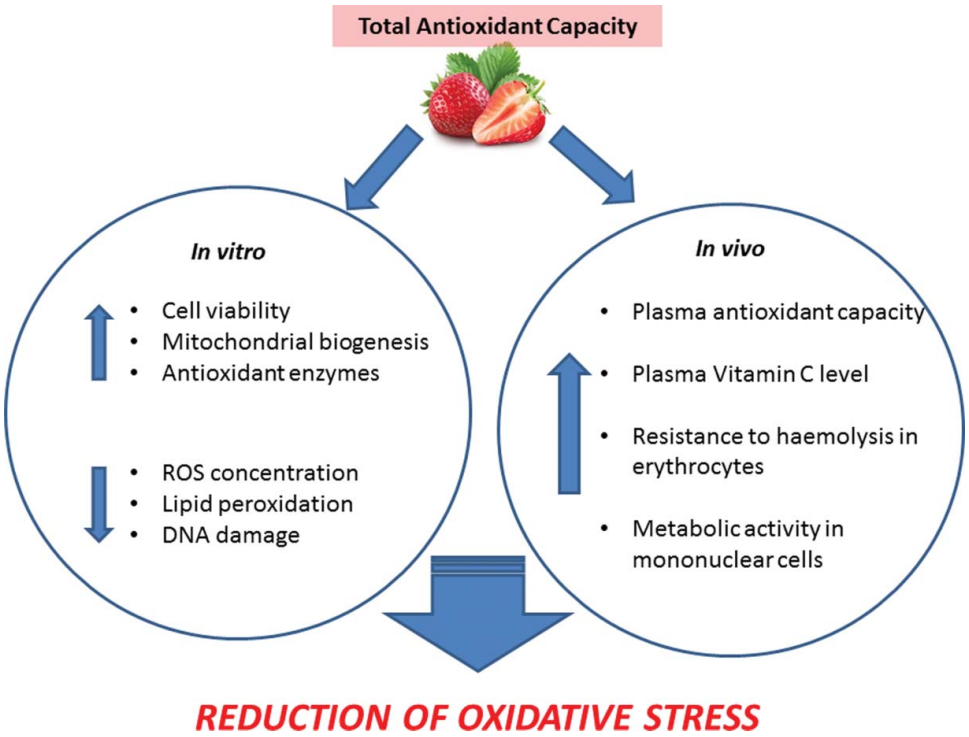


**Figure 1** Schematic representation of the *in vitro* and *in vivo* effects of strawberry total antioxidant capacity.

both in physiological and pathological conditions. For example, polyphenol consumption is efficacious in slowing the aging process in rats, through the decrease of ROS production, enhancement of antioxidant defense, and increase in mitochondrial biogenesis (Laurent et al., 2012; Charles et al., 2013; Giampieri et al., 2015b). At the same time, phenol supplementation has shown to be effective in reducing doxorubicin-induced oxidative damage, in improving antioxidant barriers as well as in restoring red blood cell and bone marrow cell counts, and also hemoglobin levels in rats (Choi et al., 2010; Benedetti et al., 2012; Diamanti et al., 2014). Berry antioxidants play a preventive role also against the development of gastric erosions, ulcerations and cancer through different mechanisms: (i) reduction in ROS levels, (ii) decrease in lipid peroxidation, (iii) increase in antioxidant enzyme activities, and (iv) attenuation of the suppression of MMP-2 activity and the translocation of nuclear factor-kappa B (NF-$\kappa$B) (Kim et al., 2011b; Alvarez-Suarez et al., 2011; Kim et al., 2013b).

The most noteworthy evidence of polyphenol supplementation in human studies has addressed the potential changes in both plasma and cellular markers of antioxidant status in young subjects. In healthy volunteers, strawberry consumption leads to significant increases in plasma total antioxidant capacity and in serum vitamin C concentration (Prior et al., 2007; Tulipani et al., 2009b; Henning et al., 2010; Romandini et al., 2013; Prymont-Przyminska et al., 2014), enhances resistance to hemolysis in erythrocytes, reduces percentage of mortality and increases the proportion of metabolic activity in mononuclear cells (Tulipani et al., 2011; Tulipani et al., 2014) (Fig. 1). Among the mechanisms of action implicated in the antioxidant effects of strawberry consumption, a reduction in the DNA oxidative damage and an improvement of the DNA repair capacity could be involved.

However, since most of the literature data have been obtained from *in vitro* studies and considering the very low polyphenol bioavailability *in vivo* (Banaszewski et al., 2013; Giampieri et al., 2014c; Giampieri et al., 2015a), their actual contribution to the overall cellular antioxidant capacity seems to be negligible. Undoubtedly, the antioxidant capacity remains an essential mechanism, but it is not able to explain the beneficial effects of polyphenols alone. Therefore, more complex mechanisms, that intertwine and complement with the antioxidant capacity, begin to be investigated (Giampieri et al., 2014c) in order to clarify the healthy effects of strawberry polyphenols against the most common chronic diseases, such as inflammation, cardiovascular diseases (CVD), metabolic syndrome, and cancer.

### *Strawberry and Anti-inflammatory Properties*

A sustained proinflammatory state is a major contributing factor to the development, progression, and complication of the most known chronic diseases such as CVD, Alzheimer's, and type 2 diabetes. In normal conditions, inflammation is the common, protective, and temporary response of the innate immune system to pathogens and injury stimuli. Quantifiable inflammatory responses are characterized by the production of pro- and anti-inflammatory cytokines which act as signals between immune cells to coordinate the inflammatory response (Joseph et al., 2014). Cytokines are small soluble proteins secreted by different cells to influence the behavior of other cells involved in cellular immunity and inflammation; they also play an important role as hormonal mediators for host defense, growth, and repair processes within injured tissues (Liu and Lin, 2012; Dia et al., 2014). Among cytokines, interleukin 1$\beta$ (IL-1 $\beta$), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-$\alpha$) are commonly induced together and act as proinflammatory and alarm cytokines. IL-1 $\beta$ is produced by activated macrophages, which sustain inflammation by promoting lymphocyte functions indirectly, while IL-6 is a cytokine produced by both immune and nonimmune cells in response to infection and injury (Dia et al., 2014). Moreover, TNF-$\alpha$, a pleiotropic cytokine produced by many cell types, including macrophages, monocytes, smooth muscle cells, lymphoid cells, and fibroblasts, when released in response to sepsis, can cause shock, disseminated intravascular coagulation, and multiorgan failure (Funakoshi-Tago et al., 2011; Dia et al., 2014). The abnormality of the TNF-$\alpha$ signaling pathway or excess production of TNF-$\alpha$ can elicit excessive inflammation: dysregulated TNF-$\alpha$ function is implicated in the pathological process of many diseases, including bacterial infection, rheumatoid arthritis, Crohn's disease, and several neurological diseases (Funakoshi-Tago et al., 2011).

In contrast, IL-10 is recognized as an anti-inflammatory cytokine produced by T helper type 2 lymphocytes, T regulatory cells, macrophages, and some B cells which inhibit the synthesis of other cytokines and macrophage functions during the late inflammation phase (Liu and Lin, 2012).

The central orchestrator of the inflammatory response is NF-$\kappa$B, a redox-sensitive transcription factor (Joseph et al., 2014). In unstimulated cells, NF-$\kappa$B remains inactive in the cytoplasm by the association with inhibitor proteins of the I$\kappa$B family, such as I$\kappa$B$\alpha$ and I$\kappa$B$\beta$. In inflammatory conditions IkB kinase is activated by pro-inflammatory stimuli and phosphorylates I$\kappa$Bs, leading to their ubiquitination and proteasomal degradation (Funakoshi-Tago et al., 2011). These events release free NF-$\kappa$B dimers in the cytosol, allowing them to translocate into the nucleus where they stimulate the expression of a wide number of genes including those responsible for the production of cytokines, chemokines (monocyte chemoattractant protein (MCP)-1), adipokines (leptin, adiponectin), cell adhesion molecules (E-selectin, P-selectin, soluble vascular cell adhesion molecule-1 (sVCAM-1)), soluble intercellular adhesion molecule-1 (sICAM-1)), and acute phase proteins (C-reactive protein (CRP), fibrinogen) (Funakoshi-Tago et al., 2011; Joseph et al., 2014).

Other important mediators of inflammation are the pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) and kinases such as mitogen-activated protein kinase (MAPK),

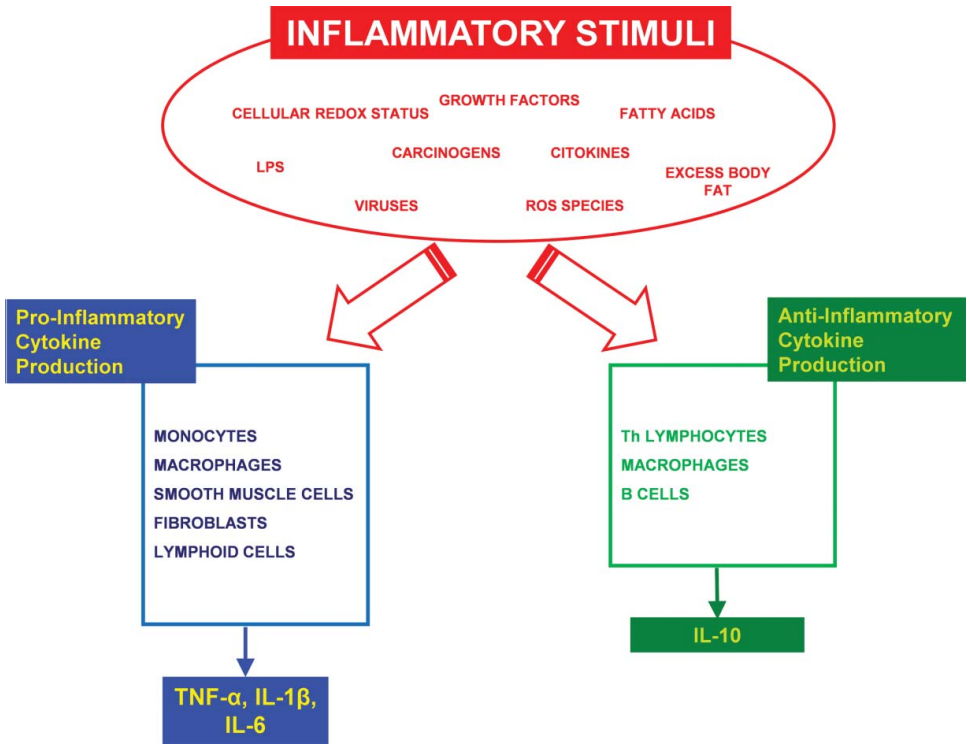


**Figure 2** Cytokine production by different stimuli.

extracellular-signal-regulated kinases (ERK), and c-Jun N-terminal kinases (JNK) that play an important role in immune responses and inflammation (Funakoshi-Tago et al., 2011; Joseph et al., 2014).

Inflammation can be triggered by stimuli such as endotoxins (i.e., lipopolysaccharide from bacteria), viruses, and changes in levels of ROS, cellular redox status, fatty acids, cytokines, growth factors, and carcinogens (Fig. 2).

In addition to classic inflammatory stimuli, inflammatory stress can also result from excess body fat and poor diet (Fig. 2). Excess body fat and obesity are associated with a concomitant and persistent increase in low-grade inflammation. In obesity, morphological changes in adipocytes result in altered secretory responses favoring an inflammatory state: expanding adipose tissue determines the production of proinflammatory proteins such as TNF-$\alpha$, IL-6, and MCP-1 by macrophages, contributing further to the proinflammatory state. Elevated circulating inflammatory proteins are in fact observed in obesity and may explain the critical link between obesity and the development of insulin resistance, type 2 diabetes, and CVD (Joseph et al., 2014).

Energy intake excess and poor dietary composition typical of the Western diet model may also promote acute (postprandial) and cumulative sustained inflammatory responses in both obese and normal weight individuals. Energy intake excess stimulates overproduction of ROS in the postprandial period, a time of active oxidative metabolism, resulting in metabolic oxidative stress and cellular redox imbalance. This change activates redox-sensitive signaling molecules, such as NF-$\kappa$B, JNK, ultimately determining an increased expression of inflammatory genes. Hence, elevations in inflammatory molecules in the postprandial state are often accompanied, and perhaps preceded, by increases in oxidative stress markers (Joseph et al., 2014). In contrast, population studies indicate that diets rich in fruits and vegetables are inversely associated with inflammatory stress (Calder et al., 2011; Nanri et al., 2011; Root et al., 2012; Anderson et al., 2012).

Therefore, identifying dietary strategies that manage the modern-day inflammatory charge may have important implications for chronic disease risk reduction and for editing dietary guidelines aimed at achieving and maintaining health. During inflammation, cells involved in the inflammatory process are recruited to the damaged site, take up oxygen, and release ROS. In addition, inflammatory cells secrete cytokine and chemokine cell mediators, which help to further recruit inflammatory cells, generating yet more ROS. Consequently, transcription factors such as NF-$\kappa$B and activator protein-1 (AP-1) that encode proinflammatory genes are activated, leading to an increased secretion of cytokines. This vicious cycle supports a protracted environment of oxidative and inflammatory stress, which contributes to several chronic diseases (Joseph et al., 2014).

Dietary polyphenols are known to act as both antioxidants and anti-inflammatory molecules (Fig. 3), thereby conferring considerable potential protective effects against development of inflammation-related chronic diseases (Giampieri et al., 2012a; Giampieri et al., 2014c; Joseph et al., 2014; Giampieri et al., 2015a).

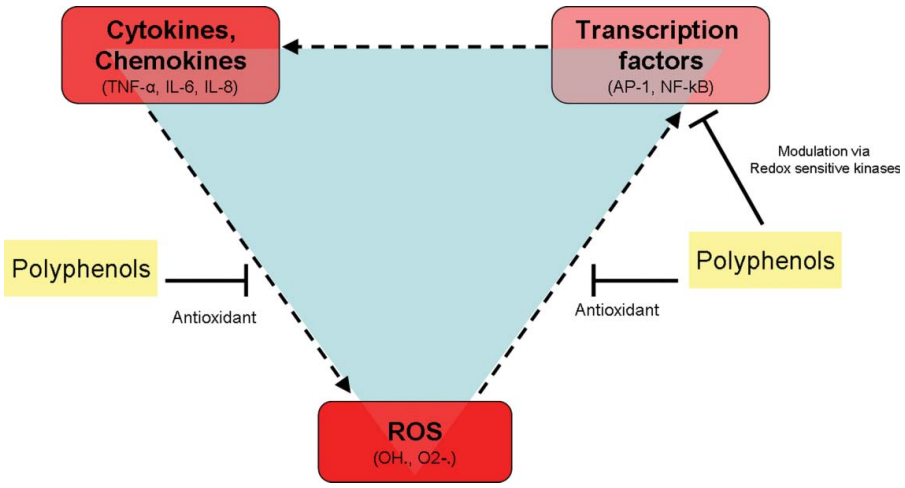


**Figure 3** Schematic representation of the linkage between antioxidant and anti-inflammatory potential of dietary polyphenols. ROS, reactive oxygen species; OH•, hydroxyl radical; O2−•, superoxide radical; AP-1, activator protein-1; NF-$\kappa$B, nuclear factor-kappa B; TNF-$\alpha$, tumor necrosis factor alpha; IL, interleukin.

Therefore, the control of excessive inflammation, through the modulation of pro- and anti-inflammatory cytokine expression in immune cells by potential food components, may represent a strategic tool to avoid immune disorder diseases and maintain health and wellness (Liu and Lin, 2012; Dia et al., 2014).

In recent years, several *in vitro* and *in vivo* studies investigating the effects of strawberries on inflammatory status have been published, underlying their inhibition on the proinflammatory cytokines. Specifically, in LPS-stressed mouse macrophages and murine primary splenocytes and peritoneal macrophages, the strawberry downregulates NF-$\kappa$B and MAPK signaling pathways (Fig. 4), leading to the reduction of cytokine levels (TNF-$\alpha$, IL-1$\beta$, and IL-6) (Liu and Lin, 2012; Liu and Lin, 2013), nitric oxide (NO) production (Dia et al., 2014), and iNOS expressions (Lee et al., 2013).

At the same time, strawberries seem to exert positive effects on the expression of anti-inflammatory cytokines: in fact in the above-mentioned cells, a significant increase in IL-10 levels has been found after strawberry treatment (Liu and Lin, 2012; Liu and Lin, 2013). Our group is currently testing the *in vitro* effects of strawberry methanolic extract in LPS-induced inflammation in human dermal fibroblast, confirming its anti-inflammatory properties: a reduction in LPS-mediated ROS and NO production and lipid and protein oxidation as well as a restoration of antioxidant enzymes and mitochondrial functionality by AMP-activated protein kinase (AMPK) pathway modulation have been found. At the same time, the

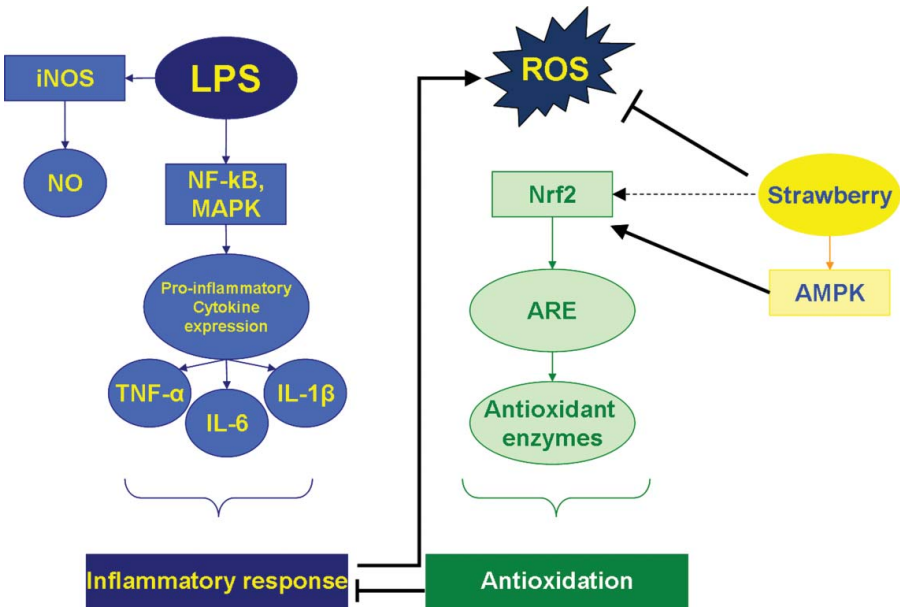


**Figure 4** Proposed mechanism of the crosstalk between different molecular pathways induced by strawberries and LPS-stimulated inflammation.

reduction in gene expression of some inflammatory-cytokines, as IL-1$\beta$, IL-6, and TNF-$\alpha$ and in their related pathways as NF-kB and iNOS have been confirmed.

*In vitro* anti-inflammatory effects have been studied also for isolated polyphenols present in the strawberry. For example, in LPS-stimulated RAW 264.7 cells (Kim et al., 2012) and in LPS-treated mouse and human phagocytes and N9 microglial cells (Gelderblom et al., 2012) fisetin, one of the most interesting polyphenol present in strawberries, exerts anti-inflammatory activities through the suppression of pro-inflammatory intracellular pathways AP-1, JNK, and NF-kB, the consequent reduction of proinflammatory cytokines (IL-6 and TNF-$\alpha$) and pro-inflammatory mediators (iNOS and COX2) and the decrease in NO formation. These findings are of considerable importance since they demonstrate that strawberries, or even pure compound, are able to exert anti-inflammatory potential by modulating the cellular pro-/anti-inflammatory cytokine secretion ratios.

Several *in vivo* studies investigating the effects of berries have been published (Joseph et al., 2014) but very little literature data takes into account the involvement of strawberries in inflammation and in its related diseases in animal and human models. In a mouse model (C57BL/6 mice) of diet-induced obesity (low-fat and high-fat diets), regular strawberries consumption contributes to the maintenance of blood glucose in obesity, and is beneficial in regulating many aspects of inflammation and inflammatory-mediated dysfunction in non-obese mice, as evidenced by the reduction of some systemic markers as CRP, plasminogen activator inhibitor (PAI-1), IL-6, and TNF-$\alpha$ (Parelman et al., 2012).

Preliminary analysis, currently performed in our lab, on Wistar rats supplemented with strawberry diet and subjected to LPS injection at the end of the experimental period, confirm the protective role of strawberries against inflammation, as demonstrated by the reduction of cytokine gene expression (IL-1$\beta$ and TNF-$\alpha$) and NO production and their related pathways (NF-kB and iNOS) in the liver, and by the restoration of biomarkers of liver injury (AST and ALT) in plasma. In addition, strawberry consumption shows protection against protein and lipid peroxidation and antioxidant enzymes and ameliorates respiratory process in isolated liver mitochondria, suggesting its beneficial effect in counteracting inflammatory condition.

The protective effect of strawberries has been also tested on platelet inflammatory mediators of atherosclerosis and thrombus formation. In C57BL/6 mice strawberry intake inhibits platelet aggregation decreasing the secretion of platelet proinflammatory molecules (as SP-selectin, SCD40L, RANTES, and IL-1$\beta$) that may play a pathogenic role in the long-term atherosclerosis process and in the triggering and propagation of acute coronary syndromes. Its protective effect on thromboembolic-related disorders may be considered a novel anti-inflammatory effect of this berry (Alarcon et al., 2015). In rats exposed to 1.5Gy irradiation of $^{56}$Fe particles that cause significant neurochemical changes in critical regions of the brain, by increasing inflammation and oxidative stress (Shukitt-Hale et al., 2013; Poulose et al., 2014) strawberry consumption reduces inflammation and pro-oxidant load in critical regions of the brain, caused by an excessive ROS production through the activation of iNOS and NADPH oxidase 2 (NOX2) (Poulose et al., 2014) and antagonizes the effects of oxidative and inflammatory signals, such as COX-2 and NF-kB (Shukitt-Hale et al., 2013). Finally, in a mouse model of stroke, fisetin inhibits the infiltration of macrophages and dendritic cells into the ischemic hemisphere and suppresses the intracerebral immune cell activation as measured by intracellular TNF$\alpha$ production, evidencing its neuroprotective effects in cerebral ischemia through the inhibition of the inflammatory response (Gelderblom et al., 2012). On the contrary, fisetin fails to exhibit inhibitory effects on carrageenan-induced paw inflammation in Jcl-ICR mice, probably due to the enhancement of MAP kinase activation by this flavanol (Funakoshi-Tago et al., 2011).

In humans, the effect of strawberry antioxidants in a milk-based beverage form on meal-induced postprandial inflammatory and insulin responses has been evaluated in a cross-over design. The postprandial test was conducted on overweight adults who consumed a high-carbohydrate, moderate-fat meal (HCFM) to induce acute oxidative and inflammatory stress, accompanied by a single serving of strawberries, a 6-week strawberry or a placebo beverage. Acute and medium strawberry consumption significantly attenuates the postprandial inflammatory response, as indicated by the reduction in CRP, IL-6, PAI-1, and IL-1$\beta$ levels and in postprandial insulin response, providing evidence for the positive effects of strawberries on postprandial inflammation and insulin sensitivity (Edirisinghe et al., 2011; Ellis et al., 2011).

Another chronic feeding study with strawberries was performed in obese individuals subjected to strawberry freeze-dried powder or control intervention for 3 weeks (Zunino et al., 2012). However, no differences in inflammatory markers (IL-1 $\beta$, IL-6, IL-8, TNF-$\alpha$, and CRP) between the two dietary groups were observed, even if a decrease in plasma concentrations of cholesterol and small HDL-cholesterol particles, and an increase of low-density lipoprotein (LDL) particle size was registered, suggesting a potential role of strawberries as a dietary instrument to reduce obesity-related disease (Zunino et al., 2012).

### *Strawberries and Anti-atherosclerotic Effects*

Obesity, type 2 diabetes mellitus and the metabolic syndrome, defined as the simultaneous occurrence of at least three of the following conditions, central or visceral obesity, hypertension, insulin resistance, high serum triglycerides, and low high-density cholesterol levels, are the main risk factors for CVD (Edirisinghe et al., 2011), which still represent the principal cause of morbidity and death worldwide (Rosamond et al., 2008; McCullough et al., 2012).

The major metabolic factor in obesity and type 2 diabetes mellitus is insulin resistance, mediated by attenuation or desensitization of insulin receptor signaling through the action of different enzymes including protein kinase B, glycogen synthase kinase-3, phosphoinositide-3 kinase, c-Jun N-terminal kinase, extracellular signal-regulated kinase, IkB kinase, and protein tyrosine phosphatase 1B (Parelman et al., 2012). Obesity is also associated with elevated circulating levels of acute-phase proteins, increased markers of endothelial dysfunction, proinflammatory cytokines, and decreased levels of anti-inflammatory cytokines. In the progression of insulin resistance to type 2 diabetes, vascular endothelium dysfunction is closely involved, as well as the development of atherosclerosis (Parelman et al., 2012). In recent years, food consumption, particularly of fruits and vegetables, has been recognized as an important dietary factor that could reduce the development of CVD incidents such as hypertension (Appel et al., 1997; Djoussé et al., 2009; Edirisinghe et al., 2011; McCullough et al., 2012), coronary heart disease, stroke (Bazzano et al., 2003), and myocardial infarction (Edirisinghe et al., 2011) (Fig. 5).

Although the mechanisms underlying the positive effects of fruits and vegetables on CVD risks reduction are not completely clear (Bazzano et al., 2003; Edirisinghe et al., 2011), some of their constituents such as fiber, potassium, magnesium, folate, and polyphenols, specially flavonoids, appear to be the responsible for them (McCullough et al., 2012). The principal mechanisms proposed for dietary flavonoids regarding CVD protection include improvement of the endothelial function through the reduction of LDL oxidation (Alvarez-Suarez et al., 2014), the inhibition of endothelial NADPH oxidase and the modulation of nitric oxide synthase activity/expression (Cassidy et al., 2013), the enhancement of plasma lipid profile, and the increase of plasma antioxidant activity (Alvarez-Suarez et al., 2014).

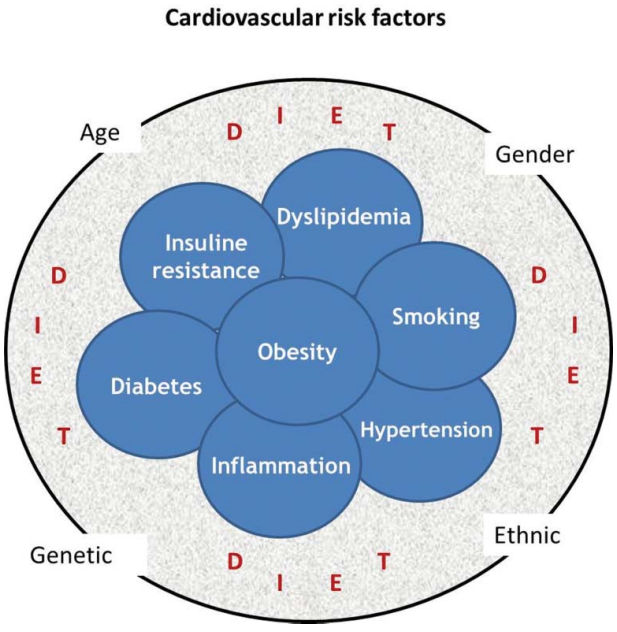


**Figure 5** Global approach of cardiovascular risk factors. Modifiable factors are represented in the inner circles, in which the diet may exert a great influence. Nonmodifiable factors are represented in the outer edge.

Among fruits, berries and their contribution in improving cardiovascular health have become a topic of great interest. They have attracted the attention of the scientific community and consumers due to their low caloric contribution, high fiber content and their natural bioactive constituents such as vitamins C and E, selenium, $\alpha$ and $\beta$ carotene, lutein, and several important polyphenols, particularly anthocyanins (Basu et al., 2010a). Indeed, berry anthocyanins may exert cardio-protective effects by (i) reducing oxidative stress and free radical generation, (ii) attenuating inflammatory gene expression via iNOS activity modulation, (iii) downregulating foam cell formation, (iv) interfering with carbohydrate digestion, (v) reducing glucose absorption, (vi) modulating dyslipidemia, and (vii) upregulating eNOS expression to maintain normal vascular function and blood pressure (Basu et al., 2010a).

Also in the particular case of strawberries, their main positive effects in the development or prevention of CVD can be summarized as three: antioxidant, antihypertensive, and antiatherosclerotic. Scientific evidence in both cellular and animal models indicates the role of strawberries in the reduction of oxidative damage and inflammation, which play a pivotal role in the initiation and progression of atherosclerosis (Basu et al., 2010b). Studies performed in different models of obesity and diabetes have shown that strawberry or purified anthocyanin supplementation can normalize blood glucose levels and limit glucose uptake and transport (Torronen et al., 2012). It has also been demonstrated that strawberries may constrain the activity of carbohydrate and lipid digestive enzymes such as $\alpha$-glucosidase and $\alpha$-amylase (Torronen et al., 2012), as well as pancreatic lipase activity and angiotensin I-converting enzyme, which may be related to the therapeutic management of hyperglycemia and hypertension (Basu and Lyons, 2012).

Moreover, data from *in vitro* experiments suggested that bioactive compounds present in strawberries, once absorbed and metabolized, could be accumulated inside the cell membrane modifying its composition, fluidity and functionality, protecting lipid bilayers against oxidative damage (Chaudhuri et al., 2007; Tulipani et al., 2011). This interaction could explain the possible *in vivo* role for strawberries in protecting LDL from oxidation (Chaudhuri et al., 2007; Tulipani et al., 2011).

Purified anthocyanins from strawberries not only regulate cholesterol distribution in human umbilical vein endothelial cells by interfering with the recruitment of TNF receptor associated factors (TRAF)-2 in lipid rafts but also prevent the development of dyslipidemia and obesity in mice fed with a high-fat diet (Basu et al., 2010b). In other animal models (obese and lean C57BL/6 mice), strawberry supplementation declines overall blood glucose concentrations independently of the content of dietary fat and reduces plasma CRP supporting a potential protective effect against cardiovascular risk.

CRP is indeed expressed in the liver and adipose tissue and is associated with increased adiposity and augmented risk for developing CVD, diabetes, and leptin resistance. Additionally, CRP is inversely correlated with adiponectin levels in obesity and the metabolic syndrome (Parelman et al., 2012).

Several human studies performed in heterogeneous populations (healthy and obese subjects, subjects with type 2 diabetes, and subjects with metabolic syndrome) have demonstrated that strawberry supplementation decreases circulating levels of CRP (Edirisinghe et al., 2011; Moazen et al., 2013) and VCAM-1 (Basu et al., 2010b; Basu et al., 2012), decreases lipid peroxidation (Moazen et al., 2013), as well as total and LDL-cholesterol (Basu et al., 2010b; Basu et al., 2012; Alvarez-Suarez et al., 2014), thus improving some atherosclerotic risk factors. The reduction of plasma lipid levels can be explained, at least in part, through the high content of dietary fiber in strawberry (2 g fiber/100 g fresh edible portion) (Zunino et al., 2012) and/or through the ability of strawberry polyphenols to activate AMPK pathway, which is related to lipid metabolism, as evidenced recently in our experiments.

Strawberry consumption also decreases glycated hemoglobin levels (Moazen et al., 2013) and increases both the mean particle size of plasma LDL which is positively associated with a decrease risk of developing CVD, type 2 diabetes mellitus, and metabolic syndrome (Zunino et al., 2012) and the lag phase duration previous to the copper-induced formation of plasma lipid oxidation products in healthy subjects modifying the plasma water-soluble and/or the lipoprotein environment (Tulipani et al., 2014). In addition, strawberry intake improves platelet function, by decreasing central clustered platelets and making them less receptive to activation stimuli (Alvarez-Suarez et al., 2014). Activation of platelets and their subsequent binding to the endothelium is a key process in the development and progression of CVD (van Gils et al., 2009). Other studies corroborate that strawberry ingestion attenuates the PAI-I, IL-1, and IL-6 response induced by HCFM protecting therefore, from the increase in thrombotic and inflammatory factors as discussed above (Ellis et al., 2011). Moreover, the decrease of the postprandial insulin response to HCFM suggests that its inclusion into diet may also reduce the insulin requirement to achieve glucose homeostasis (Edirisinghe et al., 2011).

In energy metabolism, the glucose transport across cell membranes is also fundamental. Strawberry consumption affects glucose uptake into the cells and transport to the basolateral side by inhibiting glucose transporters. The anthocyanin Pelargonidin-3-O-glucoside isolated from strawberries inhibits the lower affinity facilitated transporter (GLUT2), which is the dominant apical intestinal sugar transporter when intestinal glucose concentrations are high, and the affinity sodium dependent glucose transporter 1 (SGLT1) after dietary ingestion. Pelargonidin-3-O-glucoside can cross from the apical side into cells, and/or to the basolateral side, and consequently inhibit the GLUT2- facilitated glucose efflux on the basolateral side of the cells (Manzano et al., 2010).

After sucrose ingestion, assumption of strawberries decreases capillary and venous plasma glucose and serum insulin concentrations as well as in the glucagon-like peptide 1 (GLP-1) response, thus improving the glycemic profile (Torronen et al., 2012).

Fig. 6 summarizes the main mechanisms of action proposed for strawberry protection in CVD.

### *Strawberry and Anti-cancer Activities*

Cancer is one of the leading causes of death worldwide and about 14.1 million of new cancer cases and 8.2 million of

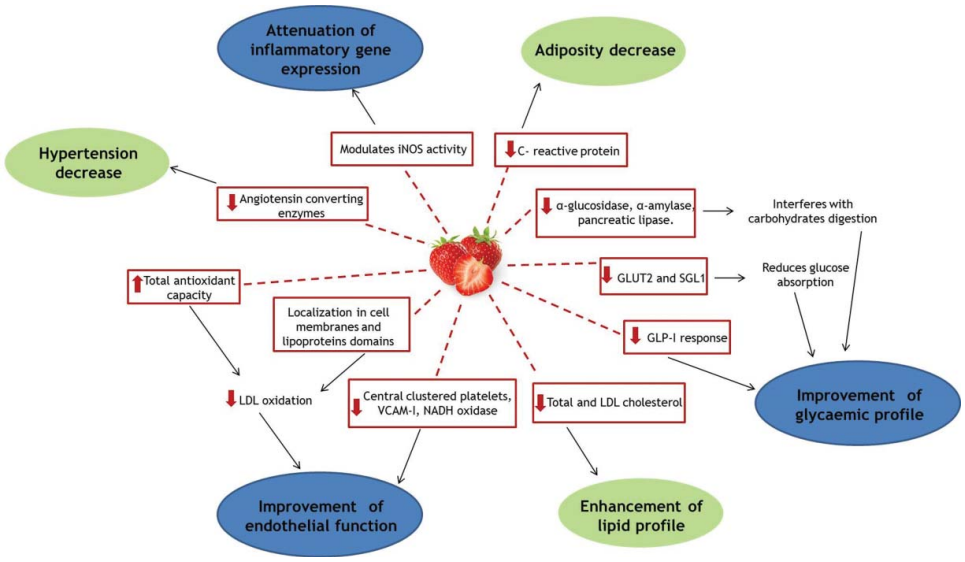


**Figure 6** Proposed mechanisms for strawberry in CVD. Dashed lines indicate the primary direct effects of strawberry action; continuous lines stand for the final effects evoked by strawberry influences on different enzymes and proteins.

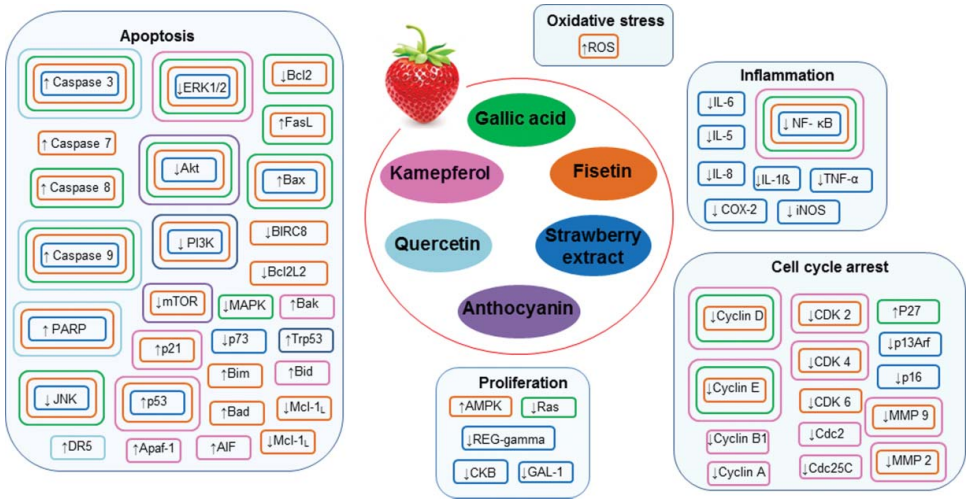


**Figure 7** Schematic representation of strawberry anti-cancer properties. Activity in the boxes reflects the effect of the compounds within the circle (each colored differently) depending on the color of the respective frames.



cancer deaths occurred in 2012 (Torre et al., 2015). Irreversible genetic damage, accumulation of mutated DNA, epigenetic alterations, microenvironmental features perpetuate cancer development, growth, infiltration, and entail metastasis through the lymphatic or circulatory systems (Eke and Cordes, 2015).

Population-based studies provide some observation of the potential protective effects of strawberry phytochemicals on the risk of particular types of cancer, which have also been postulated in several experimental cell and animal model researches (Basu et al., 2014).

Strawberry extracts, as well as purified phenols and breakdown products including tyrosol and hydroxyphenylacetic acid, show significant *in vitro* and *in vivo* anticarcinogenic activity (Fig. 7).

In HT115 and HT29 colon cancer (Brown et al., 2012), B16-F10 melanoma (Forni et al., 2014) and T47D breast cancer cells (Somasagara et al., 2012) they exert antigenotoxic, antimutagenic, and anti-invasive activities through different mechanisms: (i) modulation of cellular processes (initiation, promotion, and invasion) (Brown et al., 2012), (ii) downregulation of galectin-1 (GAL-1), proteasome activator complex subunit 3 (REG-gamma) and creatine kinase B-type (CKB) (Forni et al., 2014), (iii) induction of cytotoxicity by activation of p 53, caspase-9, -3 and poly ADP ribose polymerase (PARP1), and release of cytochrome c. Our group is currently testing the *in vitro* effects of strawberry polyphenols on two murine mammary cancer cell lines N201/1A and N201/1E, confirming their antiproliferative effects through the induction of apoptosis, increase in intracellular ROS and impairment of glycolysis and mitochondrial functionality. Some recent studies analyzed the anticancer effects of whole strawberries *in vivo* both in animals and in humans: freeze-dried strawberry consumption inhibits oral cancer development in the hamster cheek pouch model by modifying the expression of several genes, decreasing p16, p13, and Arf and increasing Trp53 level (Casto et al., 2013); at the same time, it is effective in hindering inflammation-promoted colon carcinogenesis in Crj: CD-1 Mice (Shi et al. 2015) by downregulating PI3K, Akt, ERK, and NF$\kappa$B and the expression of proinflammatory mediators (TNF-$\alpha$, IL-1$\beta$, IL-6, COX-2, and iNOS), suppressing nitrosative stress, and reducing PGE2 and total nitrite productions (Shi et al., 2015). Similarly, freeze-dried strawberry intake constrains N-nitrosomethylbenzylamine-induced esophageal cancer development in rats by regulating cytokine IL-5 and GRO/KC expression and increasing serum antioxidant capacity (Stoner et al., 2010). Strawberry aqueous extracts have been reported also to constrain tobacco-induced formation of lung tumors of Swiss ICR mice by inhibiting body weight loss, cytogenetic damage, liver degeneration, pulmonary emphysema, and lung adenomas; protective effects were more pronounced in female mice due to estrogens implicated in lung carcinogenesis metabolism (Balansky et al., 2012).

Finally, in a human phase II clinical investigation, freeze-dried strawberry powder showed a positive effect in esophageal dysplastic premalignant lesion (Chen et al., 2012), inhibiting the progression of precancerous lesions via suppression of NF-κB activation, downregulation of COX-2, and iNOS (Chen et al., 2012).

Some studies have been addressed to identify groups of flavonoids, which are responsible for cell viability decrease, cell cycle arrest, metastasis inhibition, and apoptosis induction in different cancer cells. Several strawberry flavonoids are able to arrest cell cycle by inhibition of $G_0/G_1$ and $G_2/M$ cell cycle progression, reducing matrix metalloproteinase (MMP)-2 and MMP-9 expressions and the suppression of CDK2, CDK4, cyclins B1, D1, E, A, Cdc25C, Cdc2 in colon cancer (Cho and Park, 2013), prostate cancer (Haddad et al., 2010), leukemia (Ren et al., 2010), bladder cancer (Li et al., 2011), and fibrosarcoma (Filipiak et al., 2014) (Fig. 8).

In particular, in colon cancer (Chen et al., 2010; Yu et al., 2011), in embryonal carcinoma (Tripathi et al., 2011), in PC-3 prostate cancer (Chien et al., 2010; Suh et al., 2010;) in

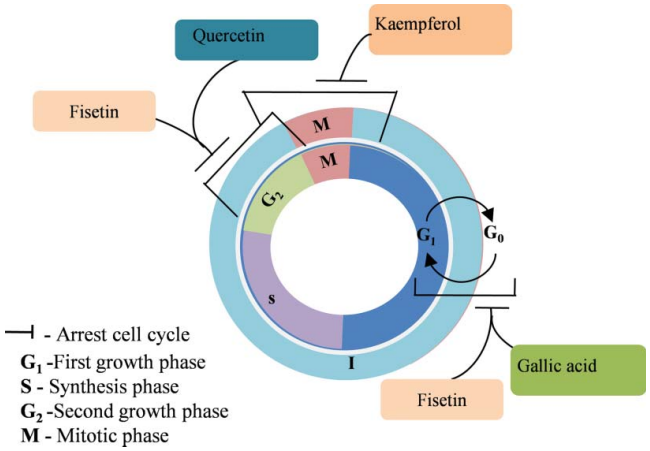


**Figure 8** Strawberry phenols arrest cell cycle in different phase.

bladder cancer (Li et al., 2011), and in multiple myeloma (Jang et al., 2012) fisetin exerts *in vitro* antiproliferative and antimetastatic effects through different mechanisms: (i) stimulation of p38 MAPK, caspase-3, and PARP and suppression of mTOR signaling, PI3-K/Akt, ERK 1/2, and JNK signaling pathways, (ii) inhibition of nuclear translocation and activation of NF-$\kappa$B and AP-1, (iii) induction of DNA fragmentation. In the same way, in human lung cancer (Suh et al., 2010; Khan et al., 2012) and in melanoma cells (Syed et al., 2012) it suppresses tumor suppressor complex 2 (TSC-2) and reduces the expressions of Raptor, Rictor, PRAS40 G$\beta$L, p70S6K, eIF-4E, and 4E-BP1. Moreover, in melanoma 451Lu cell fisetin mediates the increase in the cytosolic levels of Axin and $\beta$-transducin repeat containing protein ($\beta$-TrCP) and the decrease in the phosphorylation of glycogen synthase kinase-3 (GSK3)-$\beta$ leading to decreased $\beta$-catenin stabilization and to the disruption of Wnt/$\beta$-catenin signaling pathway; it also interferes with the functional cooperation between $\beta$-catenin and the transcription factor LEF-1/TCF-2, resulting in down-regulation of c-myc, Brn-2, and microphthalmia-associated transcription factor (Mitf) (Syed et al., 2011). On the other hand, fisetin and myricetin produce topoisomerase-mediated anticarcinogenic activity in leukemia K562 cells: fisetin behaves as a catalytic inhibitor of topo I- and topo II-DNA complexes, while myricetin induces high levels of topo-DNA complexes with topoisomerases I and II enzymes (López-Lázaro et al., 2010). Recently it has been found that fisetin can trigger a novel form of atypical apoptosis in caspase-3-deficient breast cancer MCF-7 cells through plasma membrane rupture, mitochondrial depolarization, activation of caspase-7, -8, and -9, and PARP cleavage (Yang et al., 2012).

Fisetin exerts anticancer activity also in *in vivo* models: for example, it reduces histological lesions, lipid peroxidation, and enzymatic and nonenzymatic antioxidants levels in benzo (a)pyrene exposed lung carcinogenesis in mice (Ravichandran et al., 2011), while, in combination with cyclophosphamide or with cisplatin, is effective in reducing tumor volume and microvessel density in Lewis lung carcinoma-bearing mice (Touil et al., 2011) and in embryonal carcinoma NT2/D1 mouse xenograft model (Tripathi et al., 2011).

Another important polyphenol with antiproliferative properties present in strawberries is gallic acid: in leukemia ( Lo et al., 2010; Yeh et al., 2011; Chen and Chang, 2012), osteosarcoma (Liao et al., 2012; Chen et al., 2013), and gastric cancer cells (Ho et al., 2013), it attenuates cancer invasion and migration through the suppression of JNK, Akt/ERK, PKC NF-κB pathways, and the induction of apoptosis by caspase cascade activation through the regulation of Fas/FasL, Bax, and Bcl-2 or through the dysfunction of mitochondria; at the same time it promotes the disruption of Ras and p-ERK signaling pathways in melanoma cells (Lo et al., 2010). Similarly, gallic acid and delphinidin-3-glucoside show anti-invasive and angiogenesis activities in fibrosarcoma HT1080 cells through inhibition of MMP-2 and MMP-9 proteolytic activity with the inhibition of gelatinases (Filipiak et al., 2014).

Also kempferol is a natural flavonoid present in strawberries, with antiproliferative and apoptotic activities in ovarian cancer (Luo et al., 2012) and osteosarcoma (Huang et al., 2010). Data indicate that kempferol induces intrinsic pathways of apoptosis by down-regulating the expression of Bcl-xL and upregulating p53, Bad, and Bax proteins and inhibits angiogenesis through inhibition of ERK, NF-κB, and cMyc expression in OVCAR-3 and A2780/CP70 cells (Luo et al., 2012). Furthermore, kempferol induces mitochondrial-dependent apoptotic pathway by increasing expression of cytochrome c, Apaf-1, caspase-9, -3, -7, AIF, and endoplasmic reticulum (ER)-specific pathway in U-2 OS, HOB, and 143B cell lines. A similar result has been found *in vivo* in BALB/$c^{nu/nu}$ mice model (Huang et al., 2010). The anti-cancer effects of kempferol *in vivo* have also been evaluated in colorectal cancer highlighting its capability in reducing 1,2-dimethyl hydrazine induced erythrocyte lysate and liver thiobarbituric acid reactive substances level and rejuvenating anti-oxidant enzymes catalase, superoxide dismutase, and glutathione peroxidase (Nirmala and Ramanathan, 2011). Recent evidence reveals that kempferol inhibits glucose uptake in breast cancer MCF-7 cells by increasing extracellular lactate levels due to inhibition of MCT1-mediated lactate cellular uptake and by decreasing GLUT1-mediated glucose uptake (Azevedo et al., 2015).

Finally, anthocyanins, which, as explained above, are the most important phenols present in strawberries, have recently been shown to possess anti-cancer properties: for example, they have the ability to inhibit colon cancer cells growth by activating AMPK-1 and downregulation mTOR/Akt signaling pathway (Lee et al., 2010); similar important results have been found *in vivo* in a xenograft mouse model (Lee et al., 2010).

## *CONCLUSION*

Strawberries, the most commonly consumed berry in the Mediterranean diet (Tulipani et al., 2009; Bach-Faig et al., 2011), possess an extraordinary nutritional composition due to

the high content of dietary components including vitamins, minerals folates and fibers, and are a rich source of phenolic constituents. In the past years, the first mechanism proposed to explain strawberry polyphenol effects was their antioxidant capacity, but this view is now challenged by recent findings so that more complex actions are being investigated. New studies have demonstrated that, besides being antioxidant, phenolics could interact with cellular signaling cascades regulating the activity of transcription factors and consequently affecting the expression of genes involved in cellular metabolism and cellular survival. Unfortunately, most of these data are based on *in vitro* studies, so that further *in vivo* studies are needed to translate the *in vitro* evidence into *in vivo* outcomes and to understand the mechanisms and factors governing the bioefficacy of strawberry phytochemicals.

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