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REVIEW ARTICLE

Polyphenol compounds in the chicken/animal diet: from the past to the future

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Summary

Animal feed provides a range of antioxidants that help the body building an integrated antioxidant system responsible for a prevention of damaging effects of free radicals and products of their metabolism. Vitamin E is considered to be the main chain-breaking antioxidant located in the membranes and effectively protecting them against lipid peroxidation. Recently, various polyphenol compounds, especially flavonoids, have received substantial attention because of their antioxidant activities in various *in vitro* systems. However, it was shown that flavonoid compounds are poorly absorbed in the gut and their concentrations in target tissues are too low to perform an effective antioxidant defences. The aim of the present paper is to review existing evidence about possible roles of various plant extracts provided with the diet in animal/poultry nutrition with a specific emphasis to their antioxidant activities.

Keywords polyphenolics, flavonoids, antioxidants, poultry, diet

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Introduction

Polyphenols constitute one of the most extensive groups of chemicals in the plant kingdom and more than 8000 such compounds have been isolated and described. They can be divided into three main subclasses: the flavonoids, phenolic acids and the stilbenoids. All these polyphenols are found in plants, esterified with glucose and other carbohydrates (glycosides), or as free aglycones. Polyphenols isolated from fruits, vegetables, green and black teas, herbs, roots, spices, propolis, beer and red wine are extensively researched for health-promoting potential (Szliszka and Krol, 2011). Numerous studies have demonstrated the beneficial effects of flavonoid-rich foods, including anticancer, antiinflammatory and cardiovascular protective effects, as well as a protective role in degenerative diseases (Egert and Rimbach, 2011; McCullough et al., 2012). However, positive associations between flavonoids intake and antioxidant defences *in vivo* (Duthie and Morrice, 2012) and human health (Jin et al., 2012) are not always the case.

There are two main basic questions related to polyphenols which urgently require answers. Firstly, it is necessary to understand processes of polyphenol absorption and metabolism in the body, including assessment of their availability and metabolism by gut microbiota. Generally speaking, most of polyphenolic compounds are poorly absorbed in the gut and their concentration in the target tissues is comparatively low. Secondly, more research should be conducted to understand molecular mechanisms of polyphenol action in the biological system. Initially, antioxidant properties of flavonoids attracted a substantial attention and generated a range of publications. However, recent, more comprehensive, studies indicate that antioxidant properties of polyphenol compounds are not major players in their mode of action. Nevertheless, a range of flavonoid-based products have been developed and marketed for human and some feed additives were designed for animal and poultry production. Even there were attempts in animal production to claim a possible replacement of traditional vitamin E supplementation with various plant extracts possessing antioxidant activities *in vitro*.

The aim of the present review is a critical analysis of achievements and misconceptions related to polyphenol physiological actions in poultry/animals with a specific emphasis to their antioxidant-related properties *in vivo*.

Antioxidant activities of polyphenols

Plant polyphenols can be divided into two major groups, flavonoids and non-flavonoids (Stagos et al., 2012; Table 1). Flavonoids make up the largest and the most important single group of polyphenols, and they share a common flavan core formed with 15 carbon atoms, and this class can be subdivided into several subgroups, including flavanols, anthocyanidins, flavones, flavanones and chalcones. However, laboratory and epidemiologic studies have focused on six flavonoid subgroups: flavones, flavonols, flavan-3-ols (catechins), procyanidins, flavanones and isoflavones (Theodoratou et al., 2007). The non-flavonoids contain an aromatic ring with one or more hydroxyl group and are represented by stilbene, phenolic acids, saponin and some other polyphenols. In nature, polyphenols are synthesized by plants for defence against infection and provide protective effects against stress such as ultraviolet light, pathogens and physical damage (Robbins, 2003).

Initially, molecular mechanisms of polyphenol health-promoting properties were related to their antioxidant properties. This assumption seemed to be supported by numerous model studies *in vitro* (Andriantsitohaina et al., 2012). Flavonoids can prevent injury caused by free radicals by the following mechanisms (Procházková et al., 2011): direct scavenging of reactive oxygen species (ROS), activation of antioxidant enzymes, metal chelating activity, reduction of α-tocopheryl radicals, inhibition of oxidases, mitigation of oxidative stress caused by nitric oxide, increase in uric acid levels, increase in antioxidant properties of low molecular antioxidants.

However, despite the vast amount of research, the direct antioxidant effects have been questioned (Hu, 2011):

(i) Data with model systems cannot simply be translated to the *in vivo* situation (Schewe et al., 2008). Many *in vitro*/cell culture studies on the antioxidant activity of phytochemicals employed relatively high concentrations (often in the 10–100 μM range) of the test compounds. It should be mentioned that the average concentration of most plant polyphenols in plasma rarely exceeds 1 μM in healthy subjects.

(ii) The effect of polyphenols in physiologically relevant concentrations would be relatively limited when taking into account concentrations of other antioxidants in plasma, including vitamin C (26.1–84.6 μM), vitamin E (20–30 μM), albumin and urate (several hundred μM) (Hu, 2011). Indeed, given a total antioxidant value in plasma of over 1000 μM, a minimum concentration of 20–50 μM additional antioxidant from dietary sources would be required to make a significant contribution to systemic antioxidant capacity (Halliwell et al., 2005). This is unlikely to occur, as even high intakes of dietary polyphenols typically result in unconjugated serum levels of up to 1μM. Similar situation could be found in chickens where antioxidant concentrations in

Table 1 A simplified classification of natural polyphenols (Ebrahimi and Schluesener, 2012)

Group	Class	Sub-class	Compounds
Falvo-noids	Anthocyanins		Aurantinidin, cyanidin, delphinidin, europinidin, luteolinidin, pelargonidin, malvidin, peonidin, petunidin, rosinidin, etc.
	Flavonols		3-hydroxyflavone, azaleatin, fisetin, galangin, gossypetin, kaempferide, kaempferol, isorhamnetin, morin, myricetin, natsudaidain, pachypodol, quercetin, rhamnazin, rhamnetin, etc.
	Flavones		Apigenin, luteolin, tangeritin, chrysin, 6-hydroxyflavone, baicalein, scutellarein, wogonin, diosmin, flavoxate, etc.
	Flavanones		Butin, eriodictyol, hesperetin, hesperidin, homoeriodictyol, isosakuranetin, naringenin, naringin, pinocembrin, poncirin, sakuranetin, sakuranin, sterubin, etc.
	Isoflavonoids	Isoflavones	Genistein, daidzein, lonchocarpane, laxiflorane, etc.
		Isoflavanes	Equol, etc.
	Flavanols	Monomers	Catechin, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), epigallocatechin gallate (EGCG), epiafzelechin, fisetinidol, guibourtinidol, mesquitol, robinetinidol, etc.
		Oligomers and polymers	Theaflavins, thearubigins, condensed tannins, proanthocyanidins etc.
Non-flavo-noids	Phenolic acids	Derivatives of cinnamic acid	p-coumaric acid, caffeic acid, chlorogenic acid, ferulic acid, sinapic acid, etc.
		Derivatives of benzoic acid	Gallic acid, gentisic acid, protocatechuic acid, syringic acid, vanillic acid, etc.
	Lignans		Pinoresinol, podophyllotoxin, steganacin, etc.
	Stilbenes		Resveratrol analogs, etc.

plasma are in the same range (vitamin C: 61–66 μM; Howard and Constamble, 1958; McKee et al., 1997; vitamin E: 13–15 μM, Surai, 2002; and total antioxidant value in plasma could vary from 336.9 μM, Brenes et al., 2008; up to 740-830 μM , Willemsen et al., 2011).

(iii) It is still unclear whether polyphenols have any direct antioxidant effects *in vivo*, although they might be capable of exerting such effects within the gastrointestinal tract, where polyphenols may come into direct contact with cells without having undergone absorption and metabolism (Surai et al., 2004).

(iv) Although flavonoids display potent antioxidant activity *in vitro*, the bioactive forms of flavonoids *in vivo* are not those forms found in plants (i.e. flavonoid glycosides) due to their extensive biotransformation in the small intestine and hepatic metabolism on absorption (Procházková et al., 2011). Therefore, metabolic modifications occurring *in vivo* may substantially influence the antioxidant activity of dietary flavonoids.

(v) Flavonoids are typical xenobiotics for animals and humans, metabolized as such and rapidly removed from the circulation (Natella et al., 2002).

Emerging findings suggest a large number of potential mechanisms of action of polyphenols in preventing disease, which may be beyond their conventional antioxidant activities (Rodrigo et al., 2011). Therefore, it seems likely that antioxidant activity is not a major mechanism for benefits of flavonoids on endothelial function, atherosclerosis and cardiovascular disease risk (Hodgson, 2008), as inhibition of atherosclerosis in animal models is not associated with markers of change in oxidative damage. On the other hand, there is consistent data indicating that flavonoids can enhance nitric oxide status and improve endothelial function, which may be at least partly responsible for benefits on cardiovascular health (Hodgson and Croft, 2010). Indeed, there is a shift in polyphenol-related research from testing their antioxidant activities to deeper understanding their molecular mechanisms of action including cell signalling and gene expression (Table 2).

Pro-oxidant properties of polyphenols

Chemical structure of various polyphenols indicates that they cannot only be considered purely as antioxidants, because under certain reaction conditions, they can also display pro-oxidant activity. The pro-oxidant property of dietary polyphenols may result from several possible mechanisms such as chemical instability, depletion of cellular glutathione (GSH) and mobilization of cellular copper ions (Hu, 2011). In fact, one common feature shared by several polyphenolic compounds is their sensitivity to auto-oxidation *in vitro* (Halliwell, 2007). The ability of dietary polyphenols to act as antioxidants or pro-oxidants under *in vitro* and *in vivo* conditions is dependent on a number of factors such as concentration, structure, the test system used.

It is well known that both Fe2+ and Cu+ perform Fenton-like reactions with H2O2, and polyphenol compounds containing metal binding catechol and gallol groups have very different activities, depending on the metal ion. Indeed, antioxidant activity is commonly observed for polyphenols in Fe2+/H2O2 systems, while when testing polyphenols in Cu+/H2O2 systems, pro-oxidant activity is often observed from the interactions between polyphenols and copper (Perron and Brumaghim, 2009). Ferulic and caffeic acids are hydroxycinnamic acid derivatives widely distributed in plant-derived food products, and in Fenton reaction, they behave as pro-oxidants and the possible mechanisms responsible for their pro-oxidant property may be related to their ferric reducing ability (Maurya and Devasagayam, 2010). Furthermore, any oxidized phenols (such as quinones and semiquinones) formed from phenolics during such redox reactions could also possibly be deleterious.

Table 2 Paradigm shift in flavonoid research (Schewe et al., 2008)

Concept	Current view	Traditional view
Flavonoids as radical scavengers	Minor, if at all relevant *in vivo*	Major action
Flavonoids as antioxidants	Yes, but in an indirect sense (inhibition of pro-oxidant enzymes such as NADPH oxidases, lipoxygenases and myeloperoxidase)	Major action
Flavonoids as enzyme inhibitors	Few key enzymes, particularly NADPH oxidases and angiotensin-converting enzyme	Many enzymes
Target in cell metabolism	NO* metabolism	Lipid peroxidation
Target in NO metabolism	NO* loss↓;	NOS activity↑
Role of flavonoid glucuronides	Transport metabolites in blood plasma to target cells	Urinary excretion products

In addition, some polyphenols are likely to act as pro-oxidants by forming quinones that participate in redox cycling (Bors et al., 2000). It has been shown that several polyphenols are able to bind both DNA and Cu2+ forming a ternary complex (Hadi et al., 2007). A redox reaction of the polyphenols and Cu2+ in the ternary complex may occur leading to the reduction of Cu2+ to Cu+, whose reoxidation generates a variety of ROS. It was further confirmed that the polyphenol- Cu2+ system is indeed capable of causing DNA degradation in cells such as lymphocytes, and polyphenols alone (in the absence of added copper) are also capable of causing DNA breakage in cells. It is worth mentioning that, some polyphenol compounds may follow both a redox-cycling pathway and a radical-scavenging pathway, depending on polyphenol concentration (Perron et al., 2011). A recent study gave striking evidence for *in vivo* ROS formation in human lung cancer xenograft tissues after epigallocatechin-3-gallate treatment in mice (Li et al., 2010). In fact, pro-oxidant activities of various polyphenols in cancer cells are an important feature providing their anticancer effects.

An important mechanism for flavonoid pro-oxidant toxicity involves the numerous peroxidases that catalyse the oxidation of polyphenols. For example, the oxidation of phenols by polyphenol oxidase produces extremely reactive free radical intermediates, and this may be associated with the pro-oxidant activity of polyphenols as a result of their tendency to auto-oxidation accompanied by the formation of ROS and H2O2 (Rodrigo et al., 2011). In general, it was found that the effectiveness of flavonoids for catalysing the co-oxidation of ascorbate, NADH or GSH increased as their redox potential decreased (Galati et al., 2002). Thus, the more readily oxidizable flavonoids were the most effective. In particular, it was shown that pro-oxidant properties of the flavonoids apigenin, naringenin and naringin related to the fact that their phenoxyl radicals rapidly co-oxidize glutathione (GSH) or β-nicotinamide adenine dinucleotide (NADH), resulting in extensive oxygen uptake and superoxide radical anion formation (Galati et al., 1999).

A substantial body of evidence on the pro-oxidant activity of polyphenol compounds has been accumulated. In fact, the pro-oxidant characteristic of polyphenols, related to their abilities to generate ROS, has been shown both in cell-free systems and in *in vitro* studies with cells. Reactive oxygen species have been detected in cell culture media and in phosphate buffers amended with polyphenols. For example, time-dependent generation and concentration-dependent generation of H2O2 were noted in Dulbecco's modified Eagle's medium amended with green tea, red wine, green tea polyphenol extract, black tea polyphenol extract, Ginkgo biloba extract, pomegranate extract, apple extract, epigallocatechin, epicatechin gallate, catechin gallate, theaflavin, theaflavin-3-monogallate, theaflavin-3-monogallate, theaflavin-3,3-digallate, chrysin, gallic acid and quercetin (Schweigert et al., 2001; Babich et al., 2011).

Pro-oxidant properties of polyphenols could be associated with cell signalling by which flavonoids contribute to the co-ordination of cell functions (Babich et al., 2011). Depending on the scale, pro-oxidant effects can be beneficial; as by imposing a mild degree of oxidative stress, the levels of antioxidant defences and biotransformation enzymes might be raised, leading to overall cytoprotection (Halliwell, 2008). It has been suggested that a potential health benefit for the consumption of polyphenols at dietary levels is associated with boosting antioxidant defence systems by generating low levels of ROS and inducing mild oxidative stress causing an adaptive cellular response (Moskaug et al., 2005; Lambert et al., 2010). At the other end of the scale is a toxic effect of polyphenols in humans (Mazzanti et al., 2009) and animals (Lambert et al., 2010) as a result of their pro-oxidant properties.

Polyphenol effects in poultry and farm animals

Protective effects in growing chickens of grape and grape seed extracts, by-products of juice and wine production, have been studied by a group of researchers in Spain, and the results have been published in a series of papers from the same department.

Firstly, an experiment was conducted to investigate the effect of inclusion of grape pomace (GP) at levels of 5, 15 and 30 g/kg and alpha-tocopheryl acetate (200 mg/kg) in a corn-soybean basal diet on chicken growth performance, feed digestibility and some antioxidant-related parameters in the body (Goñi et al., 2007). It has been shown that growth performance and protein and amino acid digestibilities were not affected among the different treatments. Results also showed a linear reduction of lipid oxidation in breast and thigh meats at 4 and 7 days with increasing content of GP in the diet. This research was extended and higher (60 g/kg) dose of GP was also tested (Brenes et al., 2008). The authors concentrated on protective effects of grape concentrate on the lipid peroxidation in the chicken meat during storage and showed some benefits. Furthermore, in the paper data on total antioxidant activity of the diet and excreta were presented. For example, excreta total antioxidant

activity increased from 74.7 μmol/g (control) up to 107.2 μmol/g (experimental group). However, they do not have any physiological significance, as to provide antioxidant protection in the body, an antioxidant component has to be located in a right place (e.g. in biological membranes, where peroxidation has a detrimental effect), in right concentration and in right time. Furthermore, it is surprising that the authors found increased antioxidant activity of the diet due to vitamin E supplementation [(6.29 vs. 1.87 and 11.96 vs. 8.63, Goñi et al., 2007) and (7.9 vs. 4.0 and 4.0 vs. 3.3, Brenes et al., 2008)]. In the form of tocopherol acetate, vitamin E does not possess any antioxidant activity, this puts some doubts on validity of techniques used for the assessment of antioxidant activity in the studies.

Extracts obtained from grape seeds and pomace are complex in composition and contain monomeric phenolic compounds such as (+)-catechins, (−)-epicatechin and (−)-epicatechin-3-O-gallate, and dimeric, trimeric, and tetrameric proanthocyanidins (Saito et al., 1998). It is obvious that the biological activity of these polyphenols depends on their bioavailability (Hervert-Hernández et al., 2009). It is generally accepted that the availability of phenolic compounds for human and animals is rather low. It is well known that antioxidant absorption, transport, metabolism and tissue distribution are of great importance for its protective effect (Surai, 2002). In this term, a conclusion from the paper of Brenes et al. (2008) that 'Grape pomace concentrate supplementation was as equal in antioxidant potential as vitamin E' sounds like a premature one. Similarly, a conclusion from the research conducted in the same lab that 'Grape pomace could be considered as a good alternative to α-tocopheryl acetate supplementation of feeds and to improve vitamin E status' (Goñi et al., 2007) is based just on meat stability during storage and some sparing effect of polyphenols on vitamin E level in the chicken liver is not scientifically sound for the same reason. It is well known that vitamin E possesses membrane-stabilizing effects (Surai, 2002; Surai and Fisinin, 2010) responsible for decreasing lipid peroxidation in the meat during storage. In aforementioned papers, polyphenols were not detected in tissues, and there was little research done to understand a mode of action of the grape extract at the cellular level. It is well known that lipid peroxidation in muscle depends on a range of factors, including amount and composition of lipids, composition and concentration of various natural antioxidants, activities of antioxidant enzymes and other enzymatic factors, concentration and distribution of iron and copper possessing pro-oxidant properties, etc. (Surai, 2006). None of those were studied in aforementioned papers were only final product of lipid peroxidation (MDA) and vitamin E concentration was determined.

In another publication from the same lab, it was shown that GP inclusion into the chicken diet at 30 or 60 mg/kg was associated with decreased MDA accumulation in the raw and cooked meat during storage (Sáyago-Ayerdi et al., 2009). It is important to note that in fresh meat or in the meat after 3- or 6-day storage, there was no effect of the dietary GP on lipid peroxidation. Only during longer meat storage (13 or 20 days), protective effect of dietary GB was observed. The authors suggested that polyphenols could be accumulated in tissues and provide antioxidant protection similar to vitamin E. It seems a very speculative suggestion as there are no data on polyphenol content of the meat and, generally speaking, polyphenols are not well absorbed and even if found in muscles, the active concentrations would be much lower than those providing antioxidant protection. It could well be that chelating properties of polyphenols would be responsible for changes in Fe and Cu content of the muscles leading to decrease MDA production. Therefore, mechanisms of protective effects of GP against MDA accumulation in muscles could be completely different from those described for vitamin E. It should be also mentioned that changes in total antioxidant potential of the meat extract due to dietary GP supplementation probably reflect many different changes in meat composition and without additional analysis, do not help in understanding molecular mechanisms of protective effects of dietary polyphenols.

Relationship between polyphenols and vitamin E is not straightforward and it could well be that phenolics affect vitamin redistribution between tissues and plasma. For example, it has been shown that while mice groups receiving grape extract, either isolated or in association with alpha-tocopherol, presented higher vitamin E serum levels, and their hepatic content of this vitamin was significantly lower in relation to control group (Peluzio Mdo et al., 2011). To develop this point further, it would be interesting to analyse some results on effects of polyphenolic extracts in animals. For example, it has been shown that the grape extract treatment of mice did not alter the serum and liver levels of polyphenols (Peluzio Mdo et al., 2011). It has also been shown that inclusion of Camelina meal at 2.5%, 5% and 10% increased phenolic compounds in the diet by 28.4, 31.7 and 46.4% (Aziza et al., 2010a,b). However, those phenolics most likely were not transferred to the muscles because total phenolic compounds

concentrations in breast and thigh muscles did not change and total flavonoid concentrations significantly decreased. Therefore, protective effects of the experimental diets against lipid peroxidation in the stored breast and thigh muscles are probably polyphenol-independent. It seems likely that Camelina meal, similar to other plant extracts, at high level of inclusion possesses some toxic effects. For example, for the first 21 days, FCR in birds significantly improved (from 1.83 in the control birds down to 1.71; 1.62 and 1.53, respectively, for 2.5; 5% and 10% Camelina meal consumption) (Aziza et al., 2010a). However, during 22–42 days of age, FCR dramatically increased due to Camelina meal consumption (from 1.67 in the control group up to 1.95; 1.91 and 2.0 respectively. Impaired feed conversion and decreased feed intake during the starter phase in birds fed *Camelina* cake or *Camelina* meal have been reported by Ryhanen et al. (2007) and Pekel et al. (2009).

Recent findings suggest that the grape pomace extract does not behave the same way *in vitro* and *in vivo* (Veskoukis et al., 2012). The tested grape extract exhibited potent *in vitro* antioxidant properties because it scavenged the DPPH(•) and ABTS(•+) radicals and inhibited DNA damage induced by peroxyl and hydroxyl radicals. However, administration of the extract in rats generally had a detrimental effect inducing oxidative stress at rest and after exercise, whereas exercise performance was not affected. Similarly, consuming artichoke leaf extract, a natural vegetable preparation of high antioxidant potential, resulted in higher plasma total antioxidant potential than placebo but did not limit oxidative damage to erythrocytes in competitive rowers subjected to strenuous training (Skarpanska-Stejnborn et al., 2008). In addition, supplementation with *Rhodiola rosea* extract increased total antioxidant potential in the plasma of professional rowers but had no effect on oxidative damage induced by exhaustive exercise (Skarpanska-Stejnborn et al., 2009). Despite the high antioxidant capacity of individual apple polyphenols and apple extracts and the significant antioxidant effects of apple extract added to human plasma *in vitro*, ingestion of large amounts of apples by humans does not appear to result in equivalent *in vivo* antioxidant effects of apple polyphenols (Lotito and Frei, 2004). Irrespective to antioxidant efficacy *in vitro*, black tea does not protect plasma from lipid peroxidation *in vivo* (Cherubini et al., 1999). Dietary supplementation of growing pigs with green tea polyphenols did not affect serum, liver, lung and muscle vitamin E concentrations, plasma antioxidant capacity or parameters of meat quality including meat temperature, pH, conductivity, colour and drip loss (Augustin et al., 2008). It was concluded that supplementation of pig diets with green tea catechins was not associated with improved antioxidant status and meat quality under commercial conditions.

The striking discrepancy between the *in vitro* and *ex vivo* data is most likely explained by the insufficient bioavailability of polyphenols in humans. Grape extracts are not always effective in decreasing lipid peroxidation in tissues. For example, grape seed extract (GSE) supplementation has limited protective effect in liver tissue of diabetic rats (Belviranli et al., 2012). MDA levels decreased with GSE supplementation in control rats, but increased in acute and chronic exercise groups compared with their non-supplemented control. Therefore, GSE has a limited antioxidant effect on exercise-induced oxidative stress in liver tissue. Dietary GE did not improve oxidative stress in mice as determined by plasma antioxidant potential, glutathione peroxidase and liver lipid peroxidation (Hogan et al., 2010). Natural tocopherols, rosemary, green tea, grape seed and tomato extracts were supplemented in single and in combinations at total concentrations of 100 and 200 mg/kg of feed in a 4% linseed oil-containing diet to investigate the oxidative stability of broiler breast muscle (Smet et al., 2008). Grape seed extract supplemented at 100 mg/kg showed worse results in comparison with other treatments. Unfortunately, the author did not use any control samples without inclusion of specific antioxidants into the diet, and it is impossible to judge whether there were any protective effects of extracts at the dosage of 100 mg/kg, while lipid peroxidation in the meat was lower in samples obtained from animals fed on 200 mg/kg plant extracts. However, it is not clear from the study whether the protective effect of the plant extracts was directly related to their antioxidant properties or mediated via other mechanisms of action. It is interesting to note that in a later paper by the same group of authors (Vossen et al., 2011), there was no effect of plant extracts on lipid peroxidation index (TBARS) in broiler plasma. These data support the idea that protective effect of dietary plant extract on meat oxidation was an indirect one.

In general, stabilizing effect of plant extracts or individual polyphenols is not consistent. For example, the effects of dietary tea catechins (TC) supplementation at levels of 50, 100, 200 and 300 mg/kg feed on susceptibility of chicken breast meat, thigh meat, liver and heart to iron-induced lipid oxidation were investigated (Tang et al., 2000). Tea catechins supplementation at all levels exerted antioxidative effects for all tissues with the exception of 50 mg/kg feed for breast meat, where pro-oxidant action of TC was observed.

Similarly, dietary oregano essential oil supplementation also exerted antioxidative effects, the supplementation being most effective in retarding lipid oxidation in stored raw and cooked chicken meat at the 100 mg oregano essential oil/kg feed (Botsoglou et al., 2002). There were some protective effects of dietary TC against lipid peroxidation in pig meat (Mason et al., 2005). However, dietary rosemary extract failed to show an antioxidative protective effect in pork (Haak et al., 2008). An attempt to increase oxidative stability of beef by dietary supplementation of TC or rosemary extract was not successful (O'Grady et al., 2006). In contrast, adding various extracts to the ground meat *in vitro* is proven to be more effective. For example, the control samples showed significantly higher TBARS and hexanal content over beef storage. BHA/BHT, grape seed extract, pine bark extract and oleoresin rosemary retarded the formation of TBARS by 75%, 92%, 94% and 92%, respectively, after 9 days, and significantly lowered the hexanal content throughout the storage period (Ahn et al., 2007). Indeed, when plant extracts or individual flavonoids are added to the meat, their antioxidant properties can be easily observed as there is no problem with their absorption and metabolic changes.

Detrimental effects of polyphenols

Irrespective of a great deal of information claiming health-promoting properties of various polyphenols, it should be mentioned that not all flavonoids are necessarily beneficial, and their physiological effects depend on a range factors including type, concentration, absorption and metabolic transformation, etc. Indeed, the dual role of this substance by producing either toxic or beneficial effects seems also to depend on doses and/or the experimental cell type (Hodek et al., 2002).

It should be mentioned that in some aforementioned studies, the authors did not pay much attention to the detrimental consequences of grape extract feeding. In particular, decrease chicken weight gain (by 68 g) and increase FCR (1.79 vs. 1.74), while vitamin E supplementation improved FCR (1.69 vs. 1.74). Furthermore, inclusion GPC into the chicken diet decreased fat digestibility ($p < 0.05$, at 60 g/kg), while vitamin E supplementation improved fat digestibility (86.2 vs. 84.53, $p < 0.05$) (Brenes et al., 2008). In other studies, it has been observed that condensed tannins could bind biliary salts, a limiting factor for efficient fat digestion in poultry (Krogdahl, 1985), with a concomitant reduction in their absorption and an increase in the faecal excretion in mice (Roy and Schneeman, 1981). Another mechanism whereby nutrients are rendered less digestible by polyphenols is through the inactivation of digestive enzymes. For example, proanthocyanidin extracts from bean greatly inhibited digestive enzymes (trypsin, α-amylase and lipase) in young chicks (Longstaff and McNab, 1991). Moreno et al. (2003) also demonstrated *in vitro* the inhibitory effects of grape seed extract on fat-metabolizing enzymes and lipoprotein lipase. There is some evidence to show that polyphenols can inhibit a range of enzymes including α-glucosidase and pancreatic lipase (You et al., 2011), α-amylase and α-glucosidase activity (Yilmazer-Musa et al., 2012), alpha-amylase and alpha-glucosidase (McDougall et al., 2005). The inhibition of digestive enzymes may be explained with the ability of condensed tannins to form insoluble complexes with proteins in the gastrointestinal tract (Griffiths, 1986; Horigome et al., 1988).

Binding of polyphenolic compounds to both dietary and endogenous protein, such as digestive enzymes and proteins located at the luminal side of the intestinal tract, could be a reason of the reduced apparent digestibility of protein in polyphenol-containing diets. Polyphenols can form complexes with protein due to the interaction of their reactive hydroxyl groups with the carbonyl group of protein. As a consequence of this complexation, protein and amino acid digestibility were reduced by the inclusion in chicken and pig diets of sorghum and faba bean polyphenols (Jansman et al., 1989; Ortiz et al., 1993). Some polyphenolic compounds can also reduce the absorption of iron, and possibly other trace metals, when included in a diet. For example, grape seed extract inhibited Zn absorption (Kim et al., 2011) or haeme iron absorption in a dose-dependent manner (Ma et al., 2011); (Ma et al., 2010), altered microbial protein fermentation and/or amino acid metabolism in human (Jacobs et al., 2012) or glucose uptake by intestinal cells (Johnston et al., 2005) or folic acid absorption (Lemos et al., 2007). In general, effect of polyphenol compounds on absorption and assimilation of different nutrients depends on many different factors including type of compounds, its dosage, combination with other compounds, etc. (Martel et al., 2010). The pronounced and significant growth depression was observed with the use of a grape seed extract reported by Hughes et al. (2005) and Lau and King (2003). In general, relatively high dietary concentrations of polyphenols by the addition of these ingredients reduced performance in chickens as well as other livestock (Jansman et al., 1989; Nyachotti et al., 1997).

While most flavonoids/phenolics at food/feed-derived levels are considered safe, inclusion into the diet flavonoid/phenolics-based additives needs to be assessed as there have been reports of toxic flavonoid–drug interactions, liver failure, contact dermatitis, haemolytic anaemia and oestrogenic-related concerns such as male reproductive health and breast cancer associated with dietary flavonoid/phenolic consumption or exposures (Galati and O'Brien, 2004; Mennen et al., 2005). Indeed, hazards, risks and safety of high consumption of polyphenols should always be seriously considered. In particular, Ebrahimi and Schluesener (2012) presented a range of references to the toxic effects of high doses of polyphenols, which showed that quercetin consumption is associated with chronic nephropathy in rats and reduced mice life expectancy, while green tea polyphenols disrupted kidney function in mice and enhanced tumour development in the colon of male rats. Similarly, caffeic acid induced gastrointestinal and kidney tumours in rats and mice. Other side effects of high consumption of polyphenols include thyroid toxicity, malnutrition, oestrogenic activity and infertilization. Furthermore, flavonoids could inhibit the absorption of some nutrients, interact with certain drug pharmacokinetics and affect neurobehavioral development.

Clearly, taking into account possible detrimental effects of polyphenols and their unpredicted behaviour in the body depending on the conditions (antioxidant vs. pro-oxidant, mutagen vs. antimutagen, etc.), a caution should be given for their inclusion into the diet, before enough information is available on their absorption and assimilation, pharmacokinetics and metabolic fate in the body and molecular mechanisms of their action. On the other hand, there is a need for further research in this exciting area.

Polyphenols vs. vitamin E

The main reason for vitamin E dietary supplementation for poultry and farm animals is to maintain their optimal health and high productive and reproductive performances. It includes positive effects of vitamin E on male (Surai, 1999) and female (Surai, 2002) reproduction, immunocompetence (Surai, 2002, 2006), effective growth and development (McIlroy et al., 1993), high quality of eggs and meat (Surai and Sparks, 2001; Surai and Fisinin, 2010), decreased negative consequences of various stresses (Surai and Fisinin, 2012), etc. Extensive research and wide commercial application for a number of years clearly showed essentiality of vitamin E in animal/poultry nutrition. When the idea of replacement of vitamin E by various other products, including polyphenols, is considered, it is necessary to take into account a range of physiological and biochemical functions played by these compounds. A comparison of vitamin E and polyphenol activities in animals/poultry is presented in Table 3. From the analysis presented above, it is clear that these two groups of biologically active compounds are quite different in their efficacy and mode of action. There is no sufficient evidence to indicate that polyphenols can replace vitamin E in its main biological functions. For example, some data indicating positive effects of grape extracts on meat quality are not comprehensive enough to justify such a replacement, as meat quality is only one from many important vitamin E-related issues in poultry production.

Table 3 Comparison of the mode of action of vitamin E and polyphenols

Action	Vitamin E	Plant extracts (Polyphenols)
Composition	4 tocopherols and 4 tocotrienols, tocopherol acetate is a supplement form	Thousand of various compounds with variation in composition
Absorption	Well-defined absorption in the small intestine	Poorly absorbed
Metabolic transformation within tissues	Alpha-tocopherol is an active form of vitamin E after dietary supplementation	Quickly transformed to various metabolites
Delivery to target tissues	Effectively delivered to the target tissues	Tissue concentrations are negligible
Effect on nutrient digestion	Improves digestion of many nutrients	Decrease digestion of many nutrients including protein and lipids
Specific effects on sperm function	Positive effect on male reproduction	There are no proven effects on male reproduction
Specific effects on egg/ova and female reproduction	Positive effect on female reproduction	There are no proven effects on female reproduction
Specific effects on immunity	Positive (protective) effects on the immunocompetence	Effects on the immunocompetence are not consistent
Antioxidant properties	Main chain-breaking biological antioxidant	Depending on conditions can be antioxidant or pro-oxidant
Toxicity	Low toxicity when consumed in excess	Could be toxic at high consumption

The concept of the total antioxidant system of the body (Surai, 2002, 2006; Surai et al., 2008; Surai and Fisinin, 2012) combines all the antioxidant compounds of the cell in such a way that they are effectively interacting with each other, providing an effective antioxidant defence. In this system, vitamin E has a special role being located in the biological membranes, a place where lipid peroxidation takes place. Other compounds of the antioxidant system, including polyphenols, can help vitamin E be effective by its recycling or decreasing free radical load.

It seems likely that the gut is the major place of antioxidant action of polyphenols (Surai et al., 2004). Indeed, reduction of oxidative damage, modulation of colonic flora and variation in gene expression are involved in the modulation of intestinal function by polyphenols. For example, to study the molecular effects of wine polyphenols at the gene level, the microarray technology was used: rats were treated with 50 mg/kg wine polyphenols for 14 days, mixed in the diet. Global expression analysis of 5707 genes revealed an extensive down-regulation of genes involved in a wide range of physiological functions, such as metabolism, transport, signal transduction and intercellular signalling (Dolara et al., 2005). It was shown that two major regulatory pathways were down-regulated in the colon mucosa of polyphenols-treated rats: inflammatory response and steroid metabolism.

In the last decade, studies have attempted to understand the molecular mechanism involved in polyphenol/flavonoids action. Besides scavenging free radicals, many phenolics also exhibit multiple biological properties, for example, anti-inflammatory, anticancer, antiviral, antimicrobial, vasorelaxant and anticlotting activities (Rahman et al., 2007), hepatoprotective activities, prevention of cardiovascular diseases and antitumoral effect (Sies, 2010), as well as antiprotozoans, antiulcer and gastroprotective agents, neuroprotective and antidiabetic properties (Tripoli et al., 2007). Therefore, polyphenols might exert several other specific biological effects beyond their direct antioxidant–pro-oxidant activities. This includes the inhibition of activities of different enzymes, among which telomerase, cyclooxygenase, lipoxygenase, and the interaction with signal transduction pathways and cell receptors, affecting caspase-dependent pathways, cell cycle regulation and platelet functions (D'Archivio et al., 2007; Visioli et al., 2011).

It seems likely that non-antioxidant functions of vitamin E are also of great importance for maintaining physiological and biochemical homoeostasis in the cell (Azzi, 2007; Han et al., 2010; Muyrers et al., 2010; Zingg et al., 2010, 2012; Vieira-Filho et al., 2011; Pedeboscq et al., 2012) and they cannot be performed by other compounds, including polyphenols. After 90 years of extensive research in the field of vitamin E, we greatly appreciate its unique role in biological systems, in maintaining growth, development and general health of human and animals.

Conclusions

From the data presented above it is possible to conclude

(i) Antioxidant properties of polyphenols/flavonoids observed in *in vitro* systems are convincing and in some cases, they could be even more effective than traditional biological antioxidants, including vitamins E and C.

(ii) Antioxidant activities of polyphenols/flavonoids in *in vivo* biological systems are not straightforward and depend on a variety factors including.

- Efficiency of absorption, which is generally low.
- Active concentrations in the target tissues, which are extremely low.
- Metabolic transformation after absorption which could diminish their antioxidant properties and clearly need more research.
- Surrounding environments determine whether polyphenols show antioxidant or pro-oxidant properties.
- Effect on various signalling mechanisms, including vita-gene expression.

(iii) Non-antioxidant activities of polyphenols/flavonoids seem to be more important and biologically relevant than their antioxidant activities, but need more research.

(iv) Attempts to replace vitamin E in the animal diet with various plant extracts are premature and have no scientific base to fully substantiate the claims.

(v) Effects of polyphenols/flavonoids on the gut antioxidant-pro-oxidant balance and gut health in general need further research.

(vi) Detrimental effects of polyphenols/flavonoids, including inhibitory effects on various enzymes, interference with absorption of some minerals (Zn, Cu. Fe) and vitamins need more attention and additional research.

(vii) Polyphenols/flavonoids research is an exciting area promising many discoveries in future.

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