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Review Article

Potential and challenges of tannins as an alternative to in-feed antibiotics for farm animal production

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ABSTRACT

Naturally occurring plant compounds including tannins, saponins and essential oils are extensively assessed as natural alternatives to in-feed antibiotics. Tannins are a group of polyphenolic compounds that are widely present in plant region and possess various biological activities including antimicrobial, anti-parasitic, anti-viral, antioxidant, anti-inflammatory, immunomodulation, etc. Therefore, tannins are the major research subject in developing natural alternative to in-feed antibiotics. Strong protein affinity is the well-recognized property of plant tannins, which has successfully been applied to ruminant nutrition to decrease protein degradation in the rumen, and thereby improve protein utilization and animal production efficiency. Incorporations of tannin-containing forage in ruminant diets to control animal pasture bloat, intestinal parasite and pathogenic bacteria load are another 3 important applications of tannins in ruminant animals. Tannins have traditionally been regarded as "anti-nutritional factor" for monogastric animals and poultry, but recent researches have revealed some of them, when applied in appropriate manner, improved intestinal microbial ecosystem, enhanced gut health and hence increased productive performance. The applicability of plant tannins as an alternative to in-feed antibiotics depends on many factors that contribute to the great variability in their observed efficacies.

1. Introduction

Antibiotics for growth promotion in farm animal production have been used for several decades and proved to be effective in increasing animal and poultry production efficiency. However, it is widely believed that use of antibiotics as growth promoters promotes evolution and/or selection of antibiotic-resistant microorganisms in farm animals (Chattopadhyay, 2014). Extensive researches have been done over the last couple decades to search for natural alternatives to in-feed antibiotics, and plant compounds (or phytogenic compounds) have been identified to have great potentials (Yang et al., 2015). Among them, plant tannins have received considerable attention and probably are the most studied compounds especially for farm ruminants. Biological activities of tannins and animal responses to dietary tannins have been extensively reviewed mainly focusing on animal nutrition and production (Mueller-Harvey et al., 2006; Waghorn, 2008; Wang and McAllister, 2011; Redondo et al., 2014). This review, after briefly summarizing some important chemical characteristics and biological properties of plant tannins, mainly focuses on the recent development in applications of anti-microbial, anti-parasitic and immunomodulation properties of tannins in farm animals.

2. Chemical structure and occurrence of tannins

Tannins are naturally an occurring heterogeneous group of phenolic compounds with diverse structures that share their abilities to bind and precipitate proteins. Tannins are primarily

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classified into 3 major groups: hydrolyzable tannins (HT), condensed tannins (CT) also referred as proanthocyanidins, and phlorotannins (PT). The first 2 groups are found in terrestrial plants whilst PT occur only in marine brown algae (Fig. 1). Hydrolyzable tannins are made up of a polyol core (commonly D-glucose), which is esterified with phenolic acids (mainly gallic or hexahydroxy diphenic acid). The molecular weights of HT range from 500 to 3,000 Da (Haslam, 1989). They are susceptible to hydrolysis by acids, bases or esterases, thus can be easily degraded and absorbed in the digestive tract and may cause potential toxic effects in herbivores (Dollahite et al., 1962; Mcleod, 1974). Condensed tannins are oligomeric or polymeric flavonoids consisting of flavan-3-ol units that include catechin, epicatechin, gallocatechin and epigallocatechin. Compared to HT, CT has more complex structures and higher molecular weights ranging from 1,000 to 20,000 Da. Unlike HT, only strong oxidative and acidic hydrolysis can depolymerize the CT structures that are also not susceptible to anaerobic enzyme degradation (McSweeney et al., 2001). The PT, which are structurally less complex than terrestrial tannins (HT and CT), is formed as a result of the polymerization of phloroglucinol (1,3,5-trihydroxybenzene) (Ragan and Glombitza, 1986). The molecular weights of PT range from 126 Da to 650 kDa (Targett and Arnold, 1998) and can be classified into 6 classes (Phlorethols, Isofuhalos, Echole, Fucole, Fuhalols, Fucophlorethols) based on their chemical structure. They are mainly synthesized via the acetate-malonate pathway (Herbert, 1989) although the other pathway has been proposed (Chen et al., 1997).

Tannins are widely distributed in plant kingdom, especially abundant in nutritionally important forages, shrubs, cereals and medicinal herbs (Salunkhe et al., 1982; Wang et al., 1999). They are also found in many fruit species such as banana, blackberry, apple and grape as well as tea (Nonaka et al., 1984; Bravo et al., 1992; Mertz et al., 2007; Mercurio and Smith, 2008; Kheng, 2010). Condensed tannins are the most common type of tannin in forage legumes, trees and shrubs while HT is often present in leaves of trees and browse shrubs in tropical areas (Min et al., 2003). Generally, tannins are more abundant in vulnerable parts of the plants, e.g., new leaves and flowers (Terrill et al., 1992; Van Soest, 1982; Frutos et al., 2004). The PT are concentrated in the physodes located in the cytoplasm of cells within the outer cortical layers of the thalli (Ragan and Glombitza, 1986; Lüder and Clayton, 2004; Shibata et al., 2004). Chemical structures and concentrations of tannins vary greatly among plant species, growth stages and growing conditions such as temperature, light intensity, nutrient stress and exposure to herbivory (Frutos et al., 2004; Amsler and Fairhead, 2006; Berard et al., 2011; Li et al., 2014; Huang et al., 2017).

3. Biological activity of tannins

Tannins are plant secondary metabolites that serve as a part of plant chemical defence system against invasion by pathogens and attack by insects. Tannins have shown numerous biological activities and some of them, which are most important to the modern food animal production, are summarized below.

3.1. Antimicrobial property

The antimicrobial activities of tannins have long been recognized and the toxicity of tannins to bacteria, fungi and yeasts has been reviewed (Scalbert, 1991). The mechanisms proposed so far to explain tannin antimicrobial activity include inhibition of extracellular microbial enzymes, deprivation of the substrates required for microbial growth, direct action on microbial metabolism through inhibition of oxidative phosphorylation, metal ions deprivation or formation of complexes with the cell membrane of bacteria causing morphological changes of the cell wall and increasing membrane permeability (Scalbert, 1991; Liu et al., 2013). Evidences have shown that the microbial cell membrane is the primary site of inhibitory action by tannins (Mcallister et al., 2005; Liu et al., 2013) through cell aggregation and disruption of cell membranes and functions (Fig. 2). Although protein precipitation is a universal property for all tannins, anti-microbial activity of tannins is microbial species-specific and is closely related to the chemical composition and structure of tannins. Generally, antimicrobial activity of tannins against Gram-positive bacteria has been reported to be greater than against Gram-negative bacteria (Ikigai et al., 1993; Smith and Mackie, 2004), because Gram-negative bacteria possess an outer membrane that consists of a lipid bilayer structure which is composed of an outer layer of lipopolysaccharide and proteins and an inner layer composed of phospholipids. However, tannins especially CT isolated from several plants have been shown to possess strong activity against Gram-negative bacteria. It is worth noting that pathogenic bacteria such as *Escherichia coli* O157:H7, *Salmonella, Shigella*, *Staphylococcus*, *Pseudomonas* and *Helicobacter pylori* were all sensitive to tannins (Funatogawa et al., 2004; Doss et al., 2009; Banso and Adeyemo, 2010; Liu et al., 2013). Wang et al. (2013) compared 12 tannins and found only CT isolated from purple prairie clover (*Dalea purpurea* Vent) and PT from brown alga (*Ascophyllum nodosum*) possessed strong anti-*E. coli* and anti-*E. coli* O157:H7 activity. Phlorotannins also have greater antimicrobial activity than CT and HT (Wang et al., 2009). It has been shown that number of hydroxyl groups and liberation of hydrogen peroxide upon oxidation of tannins are 2 important factors responsible for the antimicrobial properties of tannins (Akagawa et al., 2003; Smith et al., 2003; Mueller-Harvey, 2006). It has been proposed that flavonols with a trihydroxy B ring (gallocatechin) have a greater inhibitory effect on *Streptococcus*, *Clostridium*, *Proteus* and *Staphylococcus* species than catechin with a dihydroxy B ring (Sakanaka et al., 1989). Similarly, the toxicities of epi-catechin gallate and epigallocatechin gallate towards *Clostridium botulinum* were greater than those of their ungallated counterparts-epicatechin and epigallocatechin (Okuda et al., 1985). Because of the vast sources of tannins, which results in great diversity in their antimicrobial activities, screening and identification of tannins that are effective and specific to target microbes would continuously be a research endeavor.

3.2. Anti-parasitic property

Anti-parasitic properties of tannins have been demonstrated by both *in vitro* and *in vivo* studies. Condensed tannins extracted from legume tanniferous forages such as sainfoin (*Onobrychis viciifolia*), big trefoil (*Lotus pedunculatus*), birdsfoot trefoil (*Lotus corniculatus*) and sulla (*Hedysarum coronarium*) reduced the proportion of *Trichostrongylus colubriformis* hatched eggs and inhibited egg development of lungworm and gastrointestinal nematodes (mixed species of *Ostertagia*, *Oesophagostomum*, *Cooperia*, *Trichostrongylus*, and *Strongyloides*) in a dose-dependent manner (Molan et al., 2000a, 2000b, 2002). Four tropical tanniniferous plant extracts have shown anthelmintic effect on *Haemonchus contortus* and *T. colubriformis*, which mainly interfered with the process of larval exsheathment (Alonso-Díaz et al., 2008a, 2008b). Tannins extract from quebracho (Athanasiadou et al., 2001), chicory (Molan et al., 2003) and green tea (Molan et al., 2004) significantly inhibited the larval migration in a dose dependent manner. These results suggest anti-parasitic effect of tannins occurred throughout different stages of life-cycle of parasite. The anti-parasitic effects of various tannins observed in *in vitro* studies have also been confirmed in numerous *in vivo* studies involving in sheep and cattle (Paolini et al., 2003; Heckendorn et al., 2007; Chaweewan et al., 2015; Desrues et al., 2016).

The anthelmintic mechanisms of plant tannins have been suggested through "direct" action of tannins on parasite cells by 1) reducing establishment of the infective third-stage larvae in the host thereby reducing the host invasion, 2) reducing excretion of nematodes eggs by the adult worms, and 3) reducing development of eggs to third-stage larvae (Athanasiadou et al., 2001, 2005; Brunet et al., 2008; Hoste et al., 2012) and through "indirect" action by improving the host's resistance to nematodes (Coop and Kyriazakis, 2001; Min et al., 2003; Tzamaloukas et al., 2006; Pathak et al., 2016). However, similar to their antimicrobial activities, the anthelmintic effects of tannins vary greatly depending on chemical composition and structure of tannins, the parasite species or growth stages and/or the hosts' species (Hoste et al., 2006, 2012).

3.3. Antioxidant property

Naturally occurring phenolic compounds have long been recognized as effective antioxidants (Rice-Evans et al., 1995, 1996). The antioxidant property of tannins has wide application in food industry and medical field to prevent oxidative stress related diseases such as cardiovascular disease, cancer or osteoporosis (Hollman and Katan, 1999; Scalbert et al., 2005). It has been shown that CT and HT of relatively high molecular weight exhibited greater antioxidant activities than simple phenolics (Hagerman et al., 1998). The number of hydroxyl groups and the degree of polymerization of tannins are considered to be correlated with their abilities to scavenge free radicals (Ariga and Hamano, 1990). Tannins with the most hydroxyl groups are most easily oxidized (Hodnick et al., 1988) and therefore possess greatest antioxidant activity. Ricci et al. (2016) demonstrated that effectiveness of tannins as natural antioxidants is due to their complex combinations of reducing and redox activities, which also contributes to their abilities to scavenge radicals.

The potential of tannins as biological antioxidants has been indicated in many *in vitro* studies (Ho et al., 1999; Lin et al., 2001; Beninger and Hosfield, 2003; Barreira et al., 2008). The *in vivo* antioxidant activities of tannins were also demonstrated in different animal tissues. Inclusion of forage containing CT improved antioxidant status of both cattle and sheep by increasing serum antioxidant activity (Dutta et al., 2012; Dey and De, 2014; Huang et al., 2015; Peng et al., 2016). Quebracho tannins in lamb diets improved the antioxidant status of muscle (Luciano et al., 2011), liver and plasma (López-Andrés et al., 2013) and enhanced meat color stability by delaying myoglobin oxidation during refrigerated storage (Luciano et al., 2009). Given the fact that HT are degraded in the gastrointestinal tract before absorption whilst CT can not be degraded and absorbed from the digestive tract, it is not easily to explain how tannins as intact entities exert anti-oxidant activity within animal body. López-Andrés et al. (2013) found that quebracho tannins were not degraded or absorbed in the gastrointestinal tract, but increased the antioxidant capacity of liver and plasma in sheep, which demonstrated that CT may indirectly affect antioxidant status in animal tissues. The tannins-protein complexation has been shown to reduce but not eliminate the antioxidant activities of tannins (Riedl and Hagerman, 2001; Arts et al., 2002). It has been speculated that dietary tannins may spare other nutritive antioxidants during digestive process or they may protect proteins, carbohydrates, and lipids in the digestive tract from oxidative damage during digestion (Marshall and Roberts, 1990). However, the antioxidant mechanism of tannins in animal tissues is unknown. Further research in this area is needed, especially because enhancing antioxidant status is suggested to be one of the most benefits of feeding tannins to animal wellbeing and performance.

3.4. Anti-inflammatory property

Tannins possess varying anti-inflammatory activities (Mota et al., 1985; Terra et al., 2007; Sugiura et al., 2013; Park et al., 2014) that are positively associated with their antioxidant activities (Gonçalves et al., 2005; Souza et al., 2007; Park et al., 2014). *In vitro* studies have showed that tannins from grape-seed lowered low-grade inflammatory disease such as obesity by modulating cytokine expression (Terra et al., 2007; Chacón et al., 2009). Anti-inflammatory activity of CT extracted from black raspberry seeds was demonstrated by its ability to inhibit lipopolysaccharide-induced RAW 264.7 cells in producing nitric oxide (NO), a pro-inflammatory mediator that induces inflammation (Park et al., 2014). Hydrolyzable tannins from *Myricaria bracteata* showed a significant anti-inflammatory effect on croton oil-induced ear edema in mice and on collagen-induced arthritis in DBA/1 mice (Liu et al., 2015a,b). The authors speculated that the mechanism of anti-inflammatory effects was related to the potent ability for scavenging free radicals rather than inhibitory effects of HT on NO and pro-inflammatory cytokines production. Phlorotannins from *A. nodosum* and *Ecklonia cava* also exhibited potent anti-inflammatory effects based on their ability to inhibit cytokines release (Dutot et al., 2012), NO and prostaglandin-E2 productions (Wijesinghe et al., 2013). It needs to be pointed out that most of the studies in this area were conducted using *in vitro* models. The efficacy of the anti-inflammatory action of tannins in animal body after digestion needs to be evaluated further in *in vivo* model.

3.5. Anti-virus property

Tannins have been shown to have significant activity against some virus, e.g., human immunodeficiency virus (HIV), bovine adeno-associated virus and noroviruses (Uchiumi et al., 2003; Di Pasquale et al., 2012; Zhang et al., 2012). Yang et al. (2013) found that a HT (chebulagic acid) had considerable anti-enterovirus 71 activities *in vitro* and efficiently reduced mortality and relieved clinical symptoms through the inhibition of viral replication in mice model. It has been demonstrated that tannin exerted inhibitory effect on HIV-1 through inhibiting HIV-1 replication by targeting the virus reverse transcriptase (Tan et al., 1991), protease (Xu et al., 2000), and integrase (Au et al., 2001), or inhibiting HIV-1 entry into target cells by interfering with the gp41 sex-helix bundle formation (Liu et al., 2004). Epigallocatechin from green-tea was reported to inhibit hepatitis C virus (HCV) entry (Ciesek et al., 2011; Calland et al., 2012). Liu et al. (2015a,b) revealed that tannic acid (HT) inhibited HCV entry and cell-to-cell transmission but did not interfere with intracellular HCV replication. Three HT (punicalagin, punicalin and geraniin) inhibited hepatitis B virus cccDNA production via a dual mechanism through preventing the formation of cccDNA and promoting cccDNA decay (Liu et al., 2016). Ueda et al. (2013) found that tannins from persimmon (*Diospyros kaki*) significantly reduced viral infectivity of 12 tested viruses whereas tannins derived from green tea, acacia and gallnuts were effective only for some of them, and protein aggregation seems to be a fundamental mechanism underlying the anti-viral effect of persimmon tannin. Phlorotannins isolated from *E. cava* have been demonstrated to possess strong activity against influenza virus neuraminidase (Ryu et al., 2011), porcine epidemic diarrhea virus (PEDV) by inhibiting viral entry and/or viral replication (Kwon et al., 2013) and HIV-1 (Karadeniz et al., 2014). Similar antiviral activity was also demonstrated for PT isolated from *Eisenia bicyclis* against

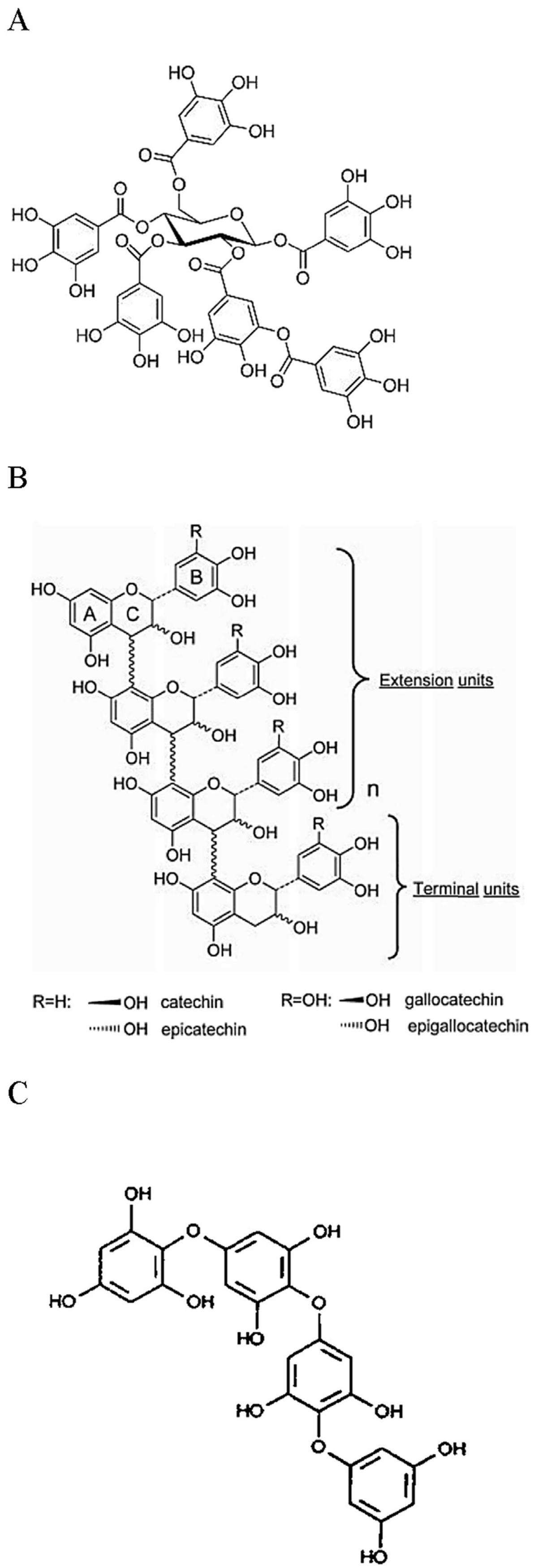

Fig. 1. Model structures of (A) hydrolyzable tannins, (B) condensed tannins and (C) phlorotannins.

murine norovirus (Eom et al., 2015) and human papilloma virus (Kim and Kwak, 2015).

All the above information demonstrated that tannins possess varying anti-virus activities depending on chemical compositions and structures. Although the mode of anti-virus action of tannins is not fully understood, information obtained so far suggested that inhibition of virus adsorption to the cells, inhibition of the virus penetration into cell nucleus and inhibition of virus reverse transcriptases might be some of the underlying mechanisms (Buzzini et al., 2008). *In vivo* studies are needed to explore the potential of tannins as natural anti-virus agents to be used in animal and poultry industries.

4. Use of tannins in ruminants

Tannins especially CT are widely distributed in nutritionally important forages, trees, shrubs and legumes, which are commonly consumed by ruminants. Therefore, the effects of CT on ruminant nutrition, health and production have been extensively studies and reviewed (Frutos et al., 2004; Mueller-Harvey, 2006; Waghorn, 2008; Patra and Saxena, 2011; Wang et al., 2015). Condensed tannins can have beneficial or detrimental effects on ruminants, depending on their amount consumed by animals, their type and chemical structure as well as the composition of the rest of the diet, especially CP concentration of the diet (Mueller-Harvey, 2006). It is generally believed that CT in temperate forage in low to medium (<50 g/kg DM) concentration benefit ruminants in terms of improving protein utilization without negatively affecting feed intake and nutrient digestion (Barry and Mcnabb, 1999; Waghorn, 2008), depending on CT source and analytical method/standard used to determine concentration. Protein precipitation capacity, anti-microbial, anti-parasitic and anti-oxidant activities are the most relevant properties of tannins to be considered for their uses in ruminant animals. By summarizing numerous researches, Waghorn (2008) has concluded that when forages are fed as a sole diet, the CT in *L. corniculatus* (about 30 g CT/kg DM) have been beneficial for ruminant production, but the CT in sainfoin, *Hedysarum coronarium* and *L. pedunculatus* (concentration generally greater than 50 g/kg DM) do not appear to benefit productivity other than by mitigating the impact of parasites. In contrast to temperate farming, the CT in browse, typical of warm and hot climates, are nearly always detrimental to ruminants, except for reducing internal parasite numbers (Waghorn, 2008). Condensed tannins at low to medium concentrations benefit ruminant production efficiency because CT reduce protein degradation in the rumen, increase the amount of dietary protein reaching small intestine for absorption (Wang et al., 1994, 1996). At high concentration, however, CT would impede feed intake due to their astringent nature and reduce protein and other nutrients digestion by “over” protecting protein, decrease rumen microbial activity and inhibit endogenous digestive enzyme activities thereby negatively affect animal performance. The dietary concentrations CT that exert the negative effective on animal performance again depend on CT sources (i.e., chemical compositions and structures). Therefore, the majority of the researches have focused on screening and evaluation of different tannins sources and to define their optimum concentrations in ruminant diets. These include to screen and identify the potential tannin-containing forages (e.g., *L. corniculatus*, *L. pedunculatus*, sainfoin) that could be incorporate into animal diets (Barry and Mcnabb, 1999; Berard et al., 2011; Acharya et al., 2013) in temperate farming, to define the optimum supplementation rates of varying external tannins (e.g., quebracho tannin, tannic acid) on animal performance (Dschaak et al., 2011; Anantasook et al., 2015; Rivera-Méndez et al., 2017) in intensive feeding operation, and to develop technologies (e.g., alkaline

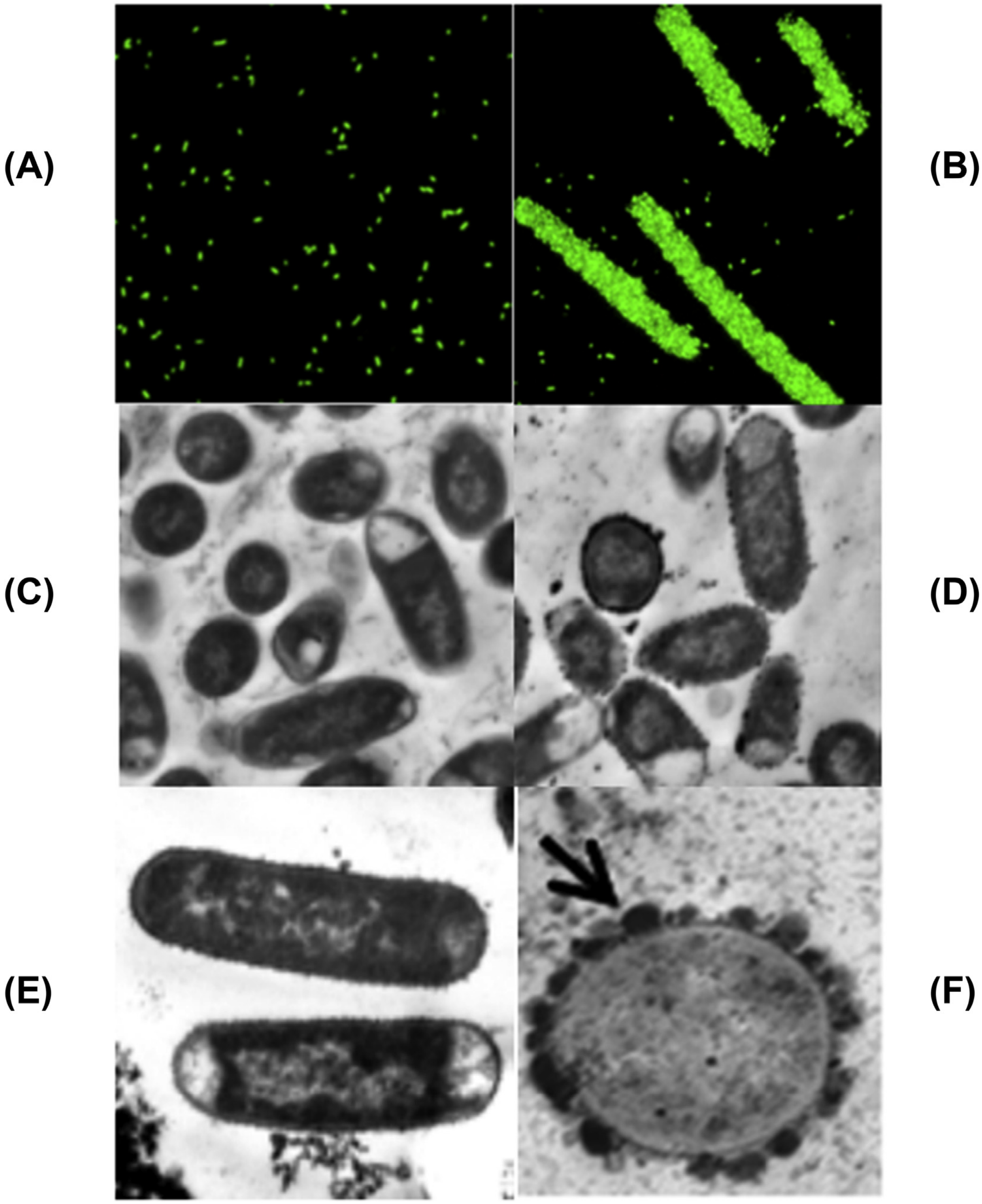

Fig. 2. Aggregation of *Escherichia coli* (strain 25922) cell incubated for 10 h with (A) 0 (Control) or (B) 200 μg/mL of condensed tannins of purple prairie clover (*Dalea purpurea* Vent.), and transmission electron micrographs of *E. coli* O157:H7 strain 3081 incubated for 24 h with (C) 0 or 50 μg/mL of (D) phlorotannins, (E) hydrolyzable tannins or (F) condensed tannins. Adapted from Wang et al. (2009, 2013) and Liu et al. (2013).

treatment, tannin-binding agent, diet mixing) in utilizing the tannin-rich tree leaves and shrubs in tropical and other areas where feed sources are limited (Murdiati et al., 1990; Smith et al., 2005; Wina et al., 2005; Brown and Ng'ambi, 2017).

Probably the most successful application of tannins in ruminant production is to reduce frothy bloat. Bloat is a common digestive disorder in ruminants. The condition is characterized by an accumulation of gas in the rumen and reticulum that can impair both digestive and respiratory function (Wang et al., 2012). Many factors can contribute to the bloat but the rapid lyses of plant cells and release of proteins from plant cells upon their entry into the rumen increasing the viscosity of the rumen fluid is a major contributing factor to pasture bloat. Tannins by precipitating protein during chewing and rumination reduce protein solubility in the rumen thereby decrease bloat occurrence. Therefore, tannins-containing forage are regarded as "bloat free". Li et al. (1996) has estimated that as little as 1.0 mg CT/g DM is needed to prevent pasture bloat. Incorporation of CT-containing forage such as sainfoin into alfalfa has been proved an effective method in controlling alfalfa pasture bloat (Fig. 3; Wang et al., 2006; Sottie et al., 2014).

Another major application of tannins in ruminants especially in grazing ruminants is to control digestive parasites. Hoste et al. (2006) have summarized *in vivo* studies that tannins in sainfoin, sulla, *L. pedunculatus*, *Sericea lespedeza*, *Acacia nilotica* and chicory had significant anthelmintic effects in digestive tract of sheep, goat and deer. External tannins such as that from mimosa (HT), chestnut

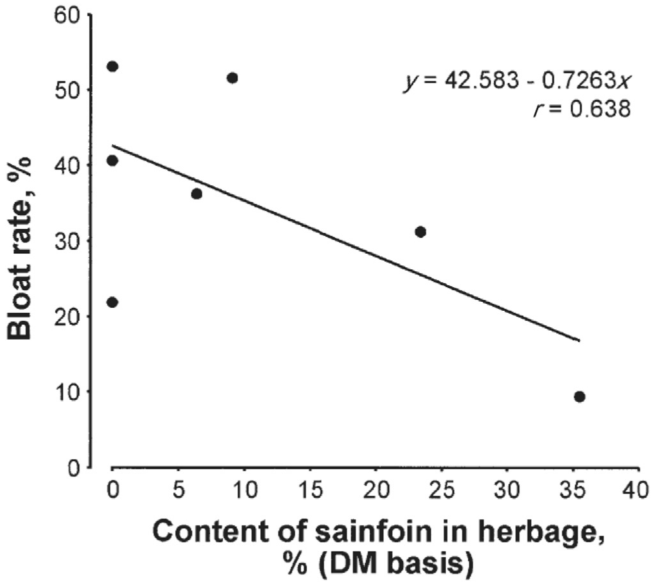

Fig. 3. Regression of bloat rate and proportion of sainfoin in herbage mass determined for beef steers (n = 12) grazing forage re-growth in 1999 and 2000 (adapted from Wang et al. (2006)).

(HT) and quebracho (CT) have been used to control various intestinal parasites in ruminant (Butter et al., 2001; Min and Hart, 2003; Min et al., 2005, 2015). It seems that dietary concentration below 20 g/kg DM of tannins is ineffective in controlling ruminant intestinal parasites. An interesting phenomenon is that sheep could detect the presence of internal parasites or associated symptoms and increase their preference for the tannin-rich feed (Lisonbee et al., 2009; Juhnke et al., 2012).

Recently, incorporation of tannins or tannin-containing forage into diets has been investigated as a pre-harvest approach to reduce foodborne pathogens in ruminant digestive tract (Table 1). Purple prairie clover has been demonstrated as a potential forage for mitigation of *E. coli* O157:H7, a deadly food-born pathogenic bacteria that reside in ruminant digestive tract (Jin et al., 2015; Huang et al., 2015). Huang et al. (2015) found that lambs challenged with *E. coli* O157:H7 fed diets containing 36 g of purple prairie clover CT/kg DM shed significant less *E. coli* O157:H7 than lambs fed diets without CT. The same CT were also demonstrated to decrease *E. coli* fecal shedding in cattle grazing native pasture containing 16 to 20 g CT/kg DM (Jin et al., 2015). In addition, adding chestnut tannin at the concentration of 15 g/kg DM decreased fecal shedding of *E. coli* for cattle fed hay diets (Min et al., 2007). However, other tannins such as that from sainfoin and *S. lespedeza* at lower concentration (<13.5 g CT/kg DM) had no effect on fecal *E. coli* shedding (Lee et al., 2009a,b; Berard et al., 2009). Supplementation of *A. nodosum* meal at the dietary concentrations of 10 to 20 g/kg DM significantly decreased *E. coli* O157:H7 fecal shedding in cattle (Table 1). Tannin concentration was not reported in these studies, but *A. nodosum* is brown algae contain high levels of PT (Wang and McAllister, 2011). These researches demonstrated that feeding plant tannins could be a practical method to effectively decrease the presence of *E. coli* O157:H7 in ruminant digestive tract thereby reduce the risk of carcass contamination and hence enhance the food safety.

5. Use of tannins in monogastric animals

Unlike for ruminants, tannins have traditionally been considered as ‘anti-nutritional’ factors in monogastric nutrition with negative effects on feed intake, nutrient digestibility and production performance (Butler, 1992; Redondo et al., 2014). Therefore, it is almost a common practice in feeding industry to minimize the use of tannin-containing feed in swine and poultry diets or to take measures to reduce their dietary concentrations if such feed are used. However, several recent reports showed that low concentrations of several tannin sources improved health status, nutrition and animal performance in monogastric farm animals (Schiavone et al., 2008; Zotte and Cossu, 2009; Biagia et al., 2010; Brus et al., 2013; Starčević et al., 2015). The mechanisms of growth-promoting effects of tannins in monogastric animal are much less understood compared with those in ruminants. Although there are some reports indicated that low concentrations of tannins increased feed intake and thus increased performance of monogastric animals, given the astringent nature of tannins, it seems not justified that this is through improving the palatability of feed. Information available to date seems to suggest that the growth-promoting action of tannins in monogastric animal relies on the balance between their negative effects on feed palatability and nutrient digestion through protein and enzyme complexation and positive effects on promoting the health status of intestinal ecosystem through their anti-microbial, anti-oxidant and anti-inflammatory activities. The final impact of tannins on animal performance depends on the type of animals and their

Table 1
Effect of dietary tannins on *Escherichia coli* and *Escherichia coli* O157:H7 fecal shedding of ruminants.

Sources	Type of tannins	Animals	Diets	Application rates	Observed effects	References
Ascophyllum nodosum extract	Phlorotannins (PT)	Feedlot cattle	Grain based diet	0, 10 or 20 g/kg diet, 14 days prior to slaughtering	Reduced fecal and hide *E. coli* and *E. coli* O157:H7	Behrends et al. (2000)
A. nodosum meal	PT	Cattle	Grain based diet	20 g/kg DM	Reduced both fecal and hide *E. coli* O157:H7 and *Salmonella*	Barham et al. (2001)
A. nodosum meal	PT	Feedlot cattle	Corn-based diet	20 g/kg diet, 14 day pre-slaughtering	Reduced *E. coli* O157:H7 prevalence on hide swabs and in fecal samples	Braden et al. (2004)
A. nodosum meal	PT	*E. coli* O157:H7 challenged cattle	Barley based concentrate diet	10 or 20 g/kg diet, up to 14 days	Reduced fecal shedding of *E. coli* O157:H7	Bach et al. (2008)
Purple prairie clover	Condensed tannins (CT)	*E. coli* O157:H7 challenged lamb	Fresh forage	36 g/kg DM ECT	Reduced *E. coli* O157:H7 fecal shedding	Huang et al. (2015)
Sericea lespedeza	CT	Goat	Hay	13.5 g/kg DM ECT	No effect on fecal *E. coli*	Lee et al. (2009a,b)
Chestnut	Hydrolyzable tannins (HT)	Cattle	Hay	15 g/day	Reduced fecal *E. coli*	Min et al. (2007)
Sainfoin	CT	Cattle	Hay/silage	1.1 to 12 g/kg DM	No effect on fecal shedding	Berard et al. (2009)
Purple prairie clover	CT	Cattle	Fresh forage	16 to 20 g/kg DM ECT	Reduced fecal *E. coli* shedding	Jin et al. (2015)

ECT = extractable condensed tannins.

physiological status, feed, type of tannins and their concentrations in the diets. Compared with other domestic animals, pigs seem to be relatively resistant to tannins in the diets, and they are able to consume relatively high quantities of tannin-rich feedstuffs without presenting any toxic symptoms (Pinna et al., 2007). This is likely due to parotid gland hypertrophy and secretion in the saliva of proline-rich proteins that bind and neutralize the toxic effects of tannins (Cappai et al., 2010, 2014). Compared to the vast sources of tannins for ruminants, sources of tannins used for monogastric animals are rather limited and so far only few have been studied and showed potential as feed additive (Table 2).

5.1. Chestnut tannins

Hydrolyzable tannins from chestnut (*Castanea sativa* Mill.) have recently been assessed as feed additive for monogastric food producing animals. Although *in vitro* studies showed strong activities against parasites and pathogens residing in animal digestive tract (Chung et al., 1998; Athanasiadou et al., 2000; Butter et al., 2001), the *in vivo* assessments have yielded inconsistent results for animal performance. At the concentrations from 0.11% to 0.45% in swine diets, it was found that chestnut HT improved feed efficiency, tended to increase viable counts of *Lactobacilli* in the jejunum and reduced caecal concentrations of ammonia, iso-butyric, and isovaleric acid, but had no effect on bacterial caecal counts, faecal excretion of *Salmonella* or colonization of the intestines (Biagia et al., 2010; Parys et al., 2010). However, increasing concentration from 0.71% to 1.5% reduced feed efficiency although feed intake, growth and carcass weight were not affected (Bee et al., 2016). Štukelj et al. (2010) reported that chestnut HT at the level of 0.15% in combination with 0.15% of a mixture of acids had no effects on health status or growth performance of pigs whereas Brus et al. (2013) found that 0.19% of it in combination with 0.16% of a mixture of acids increased growth performance, increased lactic acid bacteria and reduced *E. coli* populations in the intestines.

Schiavone et al. (2008) evaluated the effects of adding 0.15%, 0.20% and 0.25% of chestnut tannin product (77.8% HT) on growth performances of broiler chicks. The results showed that inclusion of up to 0.20% of chest nut tannin increased daily feed intake and average daily gain. However, increasing its concentration to 0.25% seemed to lead to negative effects as all the measured parameters were the lowest. Jamroz et al. (2009) assessed the effects of dietary addition of 0.025%, 0.05% and 0.1% of sweet chestnut tannins on the performance, intestinal microbial populations and histological characteristics of intestine wall in chickens. Their results showed that tannin supplementation had no effects on feed conversion and carcass quality, but tannin at 0.1% reduced final body weight and slowed down the proliferation rate in the mother-cell zone. *E. coli* and coliform bacteria in the small intestines of 28-d-old chickens were also reduced at the tannin levels of 0.05% to 0.1%. In another study, Rezar and Salobir (2014) found that addition of 0.07% and 0.2% of the same tannin product (0.05% and 0.1% HT) did not affect broiler growth performance or the organic matter, crude protein, crude ash, calcium and phosphorus balance and utilization, but increased dry matter content of excreta. In a challenged study, Tosi et al. (2013) reported that chestnut HT at the dietary concentrations of 0.71% and 1.5% reduced *Clostridium perfringens* (*Eimeria tenella, Eimeria acervulina, Eimeria maxima*) in the gut of broiler chicken orally challenged with these coccidia.

Supplementations of chestnut HT at levels of 0.45% and 0.5% also have been shown to increase live weight gain and feed intake of rabbits (Maertens and Štruklec, 2006; Zoccarato et al., 2008). However, Liu et al. (2009) found that inclusion of chestnut HT at the concentrations of 0.5% and 1.0% had no effect on growth performance of rabbits. All above information suggest that depending on the type of animals and the type of diets, dietary addition of chestnut HT at the levels lower than 0.5% for swine and rabbit and lower than 0.2% for chicken may have positive effects on their growth performance and improve intestinal health. Higher chestnut HT concentration in the diets than the above mentioned will mostly lead to decreased animal growth performance by decreasing nutrient digestion and absorption (Iji et al., 2004; Ebadi et al., 2005; Mansoori, 2009; Mansoori et al., 2015).

5.2. Grape tannins

Extracts of grape (*Vitis vinifera*) seed and grape pomace contain significant amount of polyphenolic compounds including CT (Prieur et al., 1994; Choy et al., 2014), which have been assessed for their uses as natural feed additives to monogastric food producing animals. Choy et al. (2014) reported that adding 1% of grape seed extract to pig diets increased abundances of Lachnospiraceae, *Clostridales*, *Lactobacillus* and *Ruminococcaceae* in fecal microbiome. They found that oligomers (dimer–pentamer) of grape tannin were only partially metabolized by the gut microbiota, producing phenolic metabolites that are known to be more readily absorbed. These phenolic compounds may have contributed to the altered bacterial populations thereby exerted the beneficial effects on the colon. Wang et al. (2008) found that CT in grape seed extract at the dietary concentrations from 5 to 80 mg/kg significantly decreased fecal shedding of *E. tenella*, improved antioxidant status, reduced mortality and increased growth performance of *E. tenella* infected broiler chicken and the most favorable results were observed with diets containing 10 to 20 mg CT/kg DM. Farahat et al. (2017) showed that grape seed extract possessed significant antioxidant and immunostimulant effects when fed to broiler chickens at the dietary concentrations of 0.125% to 2% with 0.125% to 0.25% being the optimum dosages. Further increasing the concentration negatively affected birds' growth performance, protein and amino acid digestion (Chamorro et al., 2013).

Grape pomace, which includes skins, pulp and contain significant amount of CT and other simple phenolic compounds, is the by-product of grape processing. Several studies evaluating the effects of grape pomace on swine and poultry performance indicated that addition of such tannin-rich product up to 10% of the diet had no effect on growth performance of broiler chicken, but enhanced anti-oxidant status and increased intestinal populations of beneficial bacteria (Brenes et al., 2008; Viveros et al., 2011; Chamorro et al., 2015). Yan and Kim (2011) showed that supplementation of a *Saccharomyces boulardii* fermented grape pomace to pig diets at the level of 0.3% improved growth performance, nutrients digestibility and altered the fatty acid pattern in the subcutaneous fat as well as some attributes of pork meat. The grape pomace was also found to improve antioxidant activity of pork and reduced the gastrointestinal absorption of mycotoxins in swine. These effects of grape pomace, however, may not be exclusively attributed to the CT because other phenolic compounds also are present in the product.

5.3. Tannic acid

Tannic acid is a HT from varying plants including tara pods (*Caesalpinia spinosa*), gallnuts from *Rhus semialata*, *Quercus infectoria* or *Sicilian Sumac* leaves (*Rhus coriaria*). Lee et al. (2010) reported that addition of tannic acid at the dietary levels of 0.0125% to 0.1% negatively impacted growth performance, hematological indices and plasma iron status of pigs, and linearly reduced faecal coliform bacteria count. However, the same authors found that feeding 0.0125% of tannic acid had no effect on growth performance, but negatively affected blood hematology and plasma Fe status when pigs were fed Fe deficient diets. It was also observed

Table 2
Applications of tannins in monogastric animals.

Sources	Type of tannins	Animals	Application rates	Effects	References
Chestnut	Hydrolyzable tannins (HT)	Gower pigs	0.15% HT + 0.15% mixture of 4 acids	No effect on health status or growth performance	Štukelj et al. (2010)
Chestnut	HT	Pigs (22 to 127 d)	0.19% HT + 0.16% of 5 acids	Increased growth performance; increased lactic acid bacteria; lowered intestinal *E. coli*	Brus et al. (2013)
Chestnut	HT	Pigs (11 to 50 kg)	0.71% and 1.5%	No effect on feed intake, body weight gain and carcass traits; reduced feed efficiency; reduced salivary and bulbourethral gland size	Bee et al. (2016)
Chestnut	HT	Pigs (8.2 to 20 kg)	0.11%, 0.23% and 0.45%	Improved feed efficiency; reduced caecal concentrations of ammonia, iso-butyric, and iso-valeric acid; NO effect on bacterial caecal counts; tended to increase viable counts of lactobacilli in the jejunum	Biagia et al. (2010)
Chestnut	HT	Pigs (6 weeks)	0.30%	No effect on faecal excretion of *Salmonella;* no effect on colonization of the intestines and internal organs	Parys et al. (2010)
Chestnut	HT	Pigs	1%, 2%, 3%	Increased small intestinal villus height, villus perimeter and mucosal thickness; reduced large intestinal mitosis and apoptosis; no effect on liver	Bilić-šobot et al. (2016)
Chestnut	HT	Broiler chicken	0.15% to 1.2%	Reduced *Clostridium perfringens* (*Eimeria tenella, Eimeria acervulina, Eimeria maxima*) in the gut	Tosi et al. (2013)
Chestnut	HT	Broiler chicken	0.15, 0.20, 0.25%	0.2% tannin improved growth performance; no effect on N balance and carcass traits	Schiavone et al. (2008)
Chestnut	HT	Laying hens (50 weeks)	0.20%	No effect on egg weights, cell thickness or yolk color; reduced cholesterol content; increased monounsaturated fatty acid	Antongiovanni et al. (2015)
Grape seeds	Condensed tannins (CT) and other phenolic compounds	Pigs (130 to 150 kg)	1%	Increased abundances of Lachnospiraceae, *Clostridales, Lactobacillus* and *Ruminococcaceae* in fecal microbial microbiome	Choy et al. (2014)
Grape seed extract	CT and other phenolic compounds	Broiler chicken	0.72%	Decreased weight gain; increased *Lactobacillus, Enterococcus* and decreased the counts of *Clostridium* in the ileal content; increased populations of *E. coli, Lactobacillus, Enterococcus,* and *Clostridium* in the cecal digesta	Viveros et al. (2011)
Grape seed extract	CT	*Eimeria tenella* challenged broiler chickens	5, 10, 20, 40, and 80 mg/kg diet	Decreased mortality and increased weight gain after the *E. tenella* infection in dose-dependent manner with 10 to 20 mg/kg yielded the best results; increased antioxidant status and improved growth performance of infected birds	Wang et al. (2008)

Table 2 (*continued*)

Sources	Type of tannins	Animals	Application rates	Effects	References
Grape seed extract	CT	Broiler chickens (0 to 42 days)	125, 250, 500, 1,000, and 2,000 mg/kg	No effect on growth performance, mortality, total lipid, high and very low-density lipoprotein cholesterols; reduced total cholesterol and low-density lipoprotein cholesterol; increased antibody titer against *Newcastle* disease virus vaccines	Farahat et al. (2017)
Grape seed extract	CT	Broiler chickens (21 days)	0.025, 0.25, 2.5 and 5.0 g/kg	5 g/kg reduced growth performance, apparent ileal digestibility of protein and amino acids; linearly decreased plasma concentrations of copper, iron and zinc; incorporation of grape seed extract in chicken diets up to 2.5 g/kg had no adverse effect on growth performance or protein and AA digestibility	Chamorro et al. (2013)
Saccharomyces boulardii fermented grape pomace	CT	Pigs (19 kg)	0.30%	30 g/kg improved the growth performance, nutrients digestibility and altered the fatty acid pattern in the subcutaneous fat as well as some attributes of pork meat	Yan and Kim (2011)
Grape pomace	CT and other phenolic compounds	Pigs	2.80%	Reduced the gastrointestinal absorption of mycotoxins; white grape pomace of *Malaysia* more effective than red grape pomace *Primitivo*	Gambacorta et al. (2016)
Grape pomace	CT	Pigs	10%	No effects on production of thiobarbituric acid reactive substances in the loin samples; increased redness of the pork	Bertol et al. (2017)
Grape pomace	CT and other phenolic compounds	Broiler chickens	6%	No effect on growth performance; increased *Lactobacillus*, *Enterococcus* and decreased the counts of *Clostridium* in the ileal content; increased populations of *E. coli*, *Lactobacillus, Enterococcus*, and *Clostridium* in the cecal digesta	Viveros et al. (2011)
Grape pomace	CT and other phenolic compounds	Broiler chickens (1 to 21 day)	5, 10%	No effect on growth performance; increased oxidative stability and polyunsaturated fatty acids content of thigh meat	Chamorro et al. (2015)
Grape pomace	CT and other phenolic compounds	Broiler chicken (21 to 42 day)	1.5%, 3%, 6% (0.22%, 0.45% and 0.9% CT)	No effect on growth performance, digestive organ sizes, and protein digestibility; increased antioxidant activity in diet, excreta, ileal content, and breast muscle	Brenes et al. (2008)
Tannic acid	HT	pigs	125, 250, 500 and 1,000 mg/kg	Reduced linearly overall average daily gain, feed efficiency and faecal coliform count	Lee et al. (2010)
Tannic acid	HT	pigs	125 mg/kg	No effect on growth performance; negatively affected blood hematology and plasma Fe status when diets are inadequate in Fe; reduced total anaerobic bacteria, *Clostridium* spp. and coliforms but increased *Bifidobacterium* spp. and *Lactobacillus* spp.	Lee et al. (2009a,b)

(*continued on next page*)

Table 2 (*continued*)

Sources	Type of tannins	Animals	Application rates	Effects	References
Tannic acid	HT	Broiler chicken (1 to 35 day)	0.50%	Increased growth performance; reduced blood glucose level; increased fat content in breast and thigh meat; reduced cholesterol content in liver	Starčević et al. (2015)
Tannic acid	HT	Broiler chicken (1 to 12 day)	0, 0.75%, or 1.5%	No effect on *Salmonella* cecal culture-positive chicks or in the numbers of *Salmonella typhimurium* in the cecal contents	Kubena et al. (2001)
Tannic acid	HT	Broiler chicken	2.5%, 3%	Reduced weight gain, protein efficiency rate and weight of bursa of Fabricius, thymus and spleen; reduced total immunoglobulin (Ig) M and IgG immunoglobulin levels and total white blood cells and absolute lymphocytes	Marzo et al. (1990)
Tannic acid	HT	Broiler chicken	1%	Decreased body weight gain and feed intake; improved the fatty acid profile of breast muscle of broilers under heat stress by decreasing monounsaturated fatty acids	Ebrahim et al. (2015)
Sweet chestnut	HT	Broiler chickens (1 to 42 day)	0.025%, 0.05%, 0.1%	No effect at 0.025% and 0.05% on growth and feed efficiency; reduced growth at 0.1%; no effect on carcass quality; reduced *E. coli* and coliform bacteria in small intestine	Jamroz et al. (2009)
Sweet chestnut	HT	Chickens (21, 23 days)	0.07%, 0.2% (0.05%, 0.15%HT)	No effects on growth performance; no effect on organic matter, crude protein, Ca and P utilization; increased dry matter content in excreta	Rezar and Salobir (2014)
Mimosa	CT	Broiler chicken (1 to 22 days)	0.5%, 1.5%, 2.0%, 2.5%	Reduced feed intake and body weight gain; improved feed efficiency at levels less than 1.5%; reduced ileal digestibility of energy, protein and amino acids; no effect on activities of pancreatic and jejunal enzymes	Iji et al. (2004)
Red quebracho (*Schinopsis lorentzii*)	CT	Challenged broiler chickens	10%	Increased body weight gain of challenged birds; increased crypt:villi ratio; decreased oocyst excretion	Cejas et al. (2011)
Acorn	HT	Pigs (14 to 28 kg)	0.516 tannic acid equivalent/kg	No effects on feed intake, improved feed efficiency; no effect on gastric mucosa	Cappai et al. (2013)

that total anaerobic bacteria, *Clostridium* spp. and coliforms were decreased but *Bifidobacterium* spp. and *Lactobacillus* spp. were increased by 0.0125% tannin acid (Lee et al., 2009a,b). Tannic acid at the concentration of 0.5% increased growth performance and fat content in breast and thigh meat, but reduced blood glucose concentration and cholesterol content in the liver of broiler chicken (Starčević et al., 2015). It is also reported that tannic acid at the dietary concentrations of 0.75% and 1.5% did not alter *Salmonella* cecal culture-positive chicks or the numbers of *Salmonella typhimurium* in the cecal contents of broiler chickens (Kubena et al., 2001). Increasing concentrations to 2.5% and 3.0% reduced weight gain and protein efficiency and impaired the immune function of growing chickens by decreasing weight of bursa of fabricius, thymus and spleen, reducing total immunoglobulin (Ig) M and IgG immunoglobulin levels and total white blood cells and absolute lymphocytes in a dose-dependent manner (Marzo et al., 1990). Ebrahim et al. (2015) found that 1% of tannic acid decreased body weight gain and feed intake but improved the fatty acid profile of breast muscle of broilers under heat stress by decreasing monounsaturated fatty acids. From above results, it seems that application rates of tannic acid in both swine and poultry are higher than those of other sources of tannins, but rarely result in positive effect on animal performance although increased antioxidant status were reported in several studies. High concentrations (e.g., $\geq$1%) appear to be toxic to animals in terms of decreasing production efficiency.

5.4. Other sources of tannins

There are a few studies that assessed several other sources of tannins for monogastric animals. Iji et al. (2004) reported that addition of mimosa (*Mimosa pudica*) tannin extract (CT) to broiler diets at the levels of 0.5%, 1.5%, 2.0%, 2.5% reduced feed intake and body weight gain but improved feed efficiency at the levels less than 1.5%. Birds fed tannin supplemented diets also reduced ileal digestibilities of energy, protein and amino acids. However, no negative effect was observed on pancreatic and jejunal enzymes activities. Cappai et al. (2014) found that supplementing acorn (*Quercus pubescens* Willd.) HT at the dietary level of 0.516 tannic acid equivalent/kg diets did not affect feed intake or gastric mucosa but improved feed efficiency. Red quebracho (*Schinopsis lorentzii*) CT was assessed for its effects on decreasing coccidiosis in *E. tenella* challenged broilers (Cejas et al., 2011). The study revealed that addition of 10% quebracho CT extract increased body weight gain of challenged birds, increased crypt:villi ratio of the intestine and decreased oocyst excretion. This study suggest that quebracho CT could be a potential prophylactic anti-coccidials agent. Zotte and Cossu, 2009 also found that 1% and 3% of red quebracho tannins improved significantly weight gain and feed conversion of rabbits in a 6-week feeding trial.

6. Challenges of using tannins as alternative to in-feed antibiotics for farm animals

Information presented above clearly demonstrate that although plant tannins possess strong anti-bacterial and anti-parasitic action *in vitro*, the observed *in vivo* effects varied greatly. Many factors, including variations of the chemical compositions of the products due to the differences in plant sources, growing conditions, processing methods as well as different application methods and feeding conditions, contribute to this vast variability. Because of the complexity of these issues, it is difficult to conduct systematic and comprehensive evaluations toward the efficacy and safety of these compounds, which undoubtedly hinders the adaptation of tannins and tannin products as a viable alternative to antimicrobial growth promoters in animal and poultry industries. Therefore, controlling this variability is the key in developing tannin products to be used as natural antimicrobial feed additives. This probably would include all procedures from production to application.

One of the reasons that medicinal plants and herbs have been used for a long history without concern of antimicrobial resistance is probably that multiple compounds presented in the formula or complex prescription act synergistically. Such synergisms among individual compounds in complex and dynamic mixtures make microorganism difficult to adapt to the multiple compounds. However, this may not be the case in prolonged use of the isolated single plant-based antimicrobial compound, which may result in the development of resistance in some microorganisms. A good example is antimalarial compound, artemisinin, in traditional Chinese medicinal plant Qinghao (*Artemisia annua* L, Asteraceae). Qinghao as a medicinal herb has been used to effectively treat malaria for a long history in Chinese medicine (Miller and Su, 2011). However, the reduction of the effectiveness of the purified form of artemisinin against malaria after using for several decades indicates that the microorganism have developed some sort of resistance to this compound. This trend is similar to the development of antibiotics resistance of bacteria. This suggests that prolonged use of plant compounds in their purified forms as antimicrobial growth promoter in animal feed has the risk to develop antimicrobial resistance. The majority of the tannins used presently in animal industry are either crude extract of mixtures of different molecular sizes or whole plant with a whole array of secondary compounds. This, coupled with the variations in chemical compositions and structures of the compounds from different sources and growing conditions, would reduce the likelihood of forming resistance by microorganisms to the complex tannins. However, little research has been done in this area and regulatory agent, scientific community and production industry need to make joint efforts to prevent microorganisms from forming resistance to tannins and other plant secondary compounds that are important to human health as this will have huge implication to humankind.

Conflict of interest

The authors declare no conflict of interest.

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References

Acharya S, Sottie E, Coulman B, Iwaasa A, Mcallister T, Wang Y, et al. New sainfoin populations for bloat-free alfalfa pasture mixtures in western Canada. Crop Sci 2013;53(5):2283–93.

Akagawa M, Shigematsu T, Suyama K. Production of hydrogen peroxide by polyphenols and polyphenol-rich beverages under quasi-physiological conditions. Biosci Biotechnol Biochem 2003;67:2632–40.

Alonso-Díaz MA, Torres-Acosta JFJ, Sandoval-Castro CA, Aguilar Caballero AJ, Hoste H. *In vitro* larval migration and kinetics of exsheathment of *Haemonchus contortus* exposed to four tropical tanniniferous plant extracts. Vet Parasitol 2008a;153:313–9.

Alonso-Díaz MA, Torres-Acosta JFJ, Sandoval-Castro CA, Brunet S, Hoste H. The effects of four tropical tanniniferous plants on the *in vitro* larval migration and kinetics of exsheathment of *Trichostrongylus colubriformis* stages. Vet Parasitol 2008b;153:187–92.

Amsler CD, Fairhead VA. Defensive and sensory chemical ecology of brown algae. Adv Bot Res 2006;43:1–91.

Anantasook N, Wanapat M, Cherdthong A, Gunun P. Effect of tannins and saponins in *Samanea saman* on rumen environment, milk yield and milk composition in lactating dairy cows. J Anim Physiol Anim Nutr Berl 2015;99:335–44.

Antongiovanni M, Minieri S, Buccioni A, Galigani I. Effect of a tannin from chestnut wood (*Castanea sativa* Miller) on cholesterol and fatty acids of eggs. 2015. http://www.wpsa.com/index.php/wpsa-proceedings/2015/xxii-european-symposium-on-the-quality-of-poultry-meat-and-the-xvi-european-symposium-on-the-quality-of-eggs-and-egg-products/2150-effect-of-a-tannin-from-chestnut-wood-castanea-sativa-miller-on-cholesterol-and-fatty-acids-of-eggs/file.

Ariga T, Hamano M. Radical scavenging action and its mode in procyanidins B-1 and B-3 from azuki beans to peroxyl radicals. Agric Biol Chem 1990;54:2499–504.

Arts MJTJ, Haenen GRMM, Wilms LC, Beetstra SAJN, Heijnen CGM, Voss HP, et al. Interactions between flavonoids and proteins: effect on the total antioxidant capacity. J Agric Food Chem 2002;50:1184–7.

Athanasiadou S, Kyriazakis I, Jackson F, Coop RL. Consequences of long-term feeding with condensed tannins on sheep parasitised with *Trichostrongylus colubriformis*. Int J Parasitol 2000;30(9):1025–33.

Athanasiadou S, Kyriazakis I, Jackson F, Coop RL. Direct anthelmintic effects of condensed tannins towards different gastrointestinal nematodes of sheep: *in vitro* and *in vivo* studies. Vet Parasitol 2001;99:205–19.

Athanasiadou S, Tzamaloukas O, Kyriazakis I, Jackson F, Coop RL. Testing for direct anthelmintic effects of bioactive forages against *Trichostrongylus colubriformis* in grazing sheep. Vet Parasitol 2005;127:233–43.

Au TK, Lam TL, Ng TB, Fong WP, Wan DC. A comparison of hiv-1 integrase inhibition by aqueous and methanol extracts of Chinese medicinal herbs. Life Sci 2001;68(14):1687–94.

Bach SJ, Wang Y, McAllister TA. Effect of seaweed (*Ascophyllum nodosum*) on fecal shedding of *Escherichia coli* O157:H7 by feedlot cattle and on growth performance of lambs. Anim Feed Sci Technol 2008;142:17–32.

Banso A, Adeyemo SO. Evaluation of antibacterial properties of tannins isolated from *Dichrostachys cinerea*. Afr J Biotechnol 2010;6(15):1785–7.

Barham AR, Barham BL, Blanton Jr JR, Allen VG, Pond KR, Miller MF. Effects of Tascor14 on prevalence levels of enterohemorragic *Escherichia* coli and *Salmonella* spp. in feedlot steers. J Anim Sci 2001;79(Suppl. 1):257.

Barreira JCM, Ferreira ICFR, Oliveira MBPP, Pereira JA. Antioxidant activities of the extracts from chestnut flower, leaf, skins and fruit. Food Chem 2008;107:1106–13.

Barry TN, Mcnabb WC. The implications of condensed tannins on the nutritive value of temperate forages fed to ruminants. Brit J Nutr 1999;81(4):263–72.

Bee G, Silacci P, Ampuero-Kragten S, Čandek-Potokar M, Wealleans AL, Litten-Brown J, et al. Hydrolysable tannin-based diet rich in gallotannins has a minimal impact on pig performance but significantly reduces salivary and bulbourethral gland size. Animal 2016. https://doi.org/10.1017/S1751731116002597.

Behrends LL, Blanton JR, Miller Jr MF, Pond KR, Allen VG. Tasco supplementation in feedlot cattle: effects on pathogen loads. J Anim Sci 2000;78(Suppl. 1):106.

Beninger CW, Hosfield GL. Antioxidant activity of extracts, condensed tannin fractions, and pure flavonoids from *Phaseolus vulgaris* L. seed coat color genotypes. J Agr Food Chem 2003;51(27):7879–83.

Berard NC, Holley RA, McAllister TA, Ominski KH, Wittenberg KM, Bouchard KS, et al. Potential to reduce *Escherichia coli* shedding in cattle feces by using sainfoin (*Onobrychis viciifolia*) forage, tested *in vitro* and *in vivo*. Appl Environ Microbiol 2009;75:1074–9.

Berard NC, Wang Y, Wittenberg KM, Krause DO, Coulman BE, McAllister TA, et al. Condensed tannin concentrations found in vegetative and mature forage legumes grown in western Canada. Can J Plant Sci 2011;91:669–75.

Bertol TM, Ludke JV, de Campos RML, Kawski VL, Junior AC, de Figueiredo EAP. Inclusion of grape pomace in the diet of pigs on pork quality and oxidative stability of omega-3 enriched fat. Ciência Rural 2017;47(4), e20150358.

Biagia G, Cipollini I, Paulicks BR, Roth FX. Effect of tannins on growth performance and intestinal ecosystem in weaned piglets. Arch Anim Nutr 2010;64(2):121.

Bilićšobot D, Kubale V, Škrlep M, ČandekPotokar M, Prevolnik PM, Fazarinc G, et al. Effect of hydrolysable tannins on intestinal morphology, proliferation and apoptosis in entire male pigs. Arch Anim Nutr 2016;70(5):378.

Braden KW, Vg JA, Pond KR, Miller MF. *Ascophyllum nodosum* supplementation: a preharvest intervention for reducing *Escherichia coli* O157:H7 and *salmonella* spp. in feedlot steers. J Food Prot 2004;67(9):1824–8.

Bravo L, Saura-Calixto F, Goni I. Effects of dietary fibre and tannins from apple pulp on the composition of faeces in rats. Brit J Nutr 1992;67(3):463–73.

Brenes A, Viveros A, Goñi I, Centeno C, Sáyago-Ayerdy SG, Arija I, et al. Effect of grape pomace concentrate and vitamin E on digestibility of polyphenols and antioxidant activity in chickens. Poult Sci 2008;87(2):307–16.

Brown D, Ng'Ambi JW. Effect of polyethylene glycol 4000 supplementation on the performance of yearling male Pedi goats fed dietary mixture levels of Acacia karroo leaf meal and Setaria verticillata grass hay. Trop Anim Health Prod 2017;49:1051–7.

Brunet S, Martinez-Ortiz-De-Montellano C, Torres-Acosta JFJ, Sandoval-Castro CA, Aguilar-Caballero AJ, Capetillo-Leal CM, et al. Effect of the consumption of Lysiloma, latisilliquumon the larval establishment of parasitic nematodes in goats. Vet Parasitol 2008;157:81–8.

Brus M, Dolinšek J, CenCič A, Škorjanc D. Effect of chestnut (*Castanea sativa* Mill.) wood tannins and organic acids on growth performance and faecal microbiota of pigs from 23 to 127 days of age. Bulg J Agric Sci 2013;19:841–7.

Butler LG. Antinutritional effects of condensed and hydrolyzable tannins. Basic Life Sci 1992;59:693–8.

Butter NL, Dawson JM, Wakelin D, Buttery PJ. Effect of dietary condensed tannins on gastrointestinal nematodes. J Agric Sci 2001;137:461–9.

Buzzini P, Arapitsas PM, Branda E, Turchetti B, Pinelli P, Ieri F, et al. Antimicrobial and antiviral activity of hydrolysable tannins. Mini Rev Med Chem 2008;8(12):1179–87.

Calland N, Albecka A, Belouzard S, Wychowski C, Duverlie G, Descamps V, et al. (-)-Epigallocatechin-3-gallate is a new inhibitor of hepatitis C virus entry. Hepatology 2012;55:720–9.

Cappai MG, Wolf P, Pinna W, Kamphues J. Pigs use endogenous proline to cope with acorn (quercus pubescens willd.) combined diets high in hydrolysable tannins. Livest Sci 2013;155(2–3):316–22.

Cappai MG, Wolf P, Dimauro C, Pinna W, Kamphues J. The bilateral parotidomegaly (hypertrophy) induced by acorn consumption in pigs is dependent on individual's age but not on intake duration. Livest Sci 2014;167:263–8.

Cappai MG, Wolf P, Große Liesner V, Kastner A, Nieddu G, Pinna W, et al. Effect of whole acorns (*Quercus pubescens*) shred based diet on parotid gland in growing pigs in relation to tannins. Livest Sci 2010;134:183–6.

Cejas E, Pinto S, Prosdocimo F, Batalle M. Evaluation of quebracho red wood (*Schinopsis lorentzii*) polyphenolic vegetable extract for the reduction of coccidiosis in broiler chicks. Int J Poult Sci 2011;10(5):344–9.

Chamorro S, Viveros A, Centeno C, Romero C, Arija I, Brenes A. Effects of dietary grape seed extract on growth performance, amino acid digestibility and plasma lipids and mineral content in broiler chicks. Animal 2013;7(4):555–61.

Chamorro S, Viveros A, Reboľe A, Rica BD, Arija I, Brenes A. Influence of dietary enzyme addition on polyphenol utilization and meat lipid oxidation of chicks fed grape pomace. Food Res Int 2015;73:197–203.

Chacón MR, Ceperuelomallafré V, Maymómasip E, Mateosanz JM, Arola L, Guitiérrez C, et al. Grape-seed procyanidins modulate inflammation on human differentiated adipocytes *in vitro*. Cytokine 2009;47(2):137–42.

Chattopadhyay MK. Use of antibiotics as feed additives: a burning question. Front Microbiol 2014;5:334.

Chen Y, Yan X, Fan X. A hypothesis on phaeophyceae polyphenols, their structural unit and mechanism of the formation (in Chinese with English summary). Oceanol Limnol Sin 1997;28:225–32.

Choy YY, Quiferrada P, Holstege DM, Frese SA, Calvert CC, Mills DA, et al. Phenolic metabolites and substantial microbiome changes in pig feces by ingesting grape seed proanthocyanidins. Food Funct 2014;5(9):2298.

Chung KT, Lu Z, Chou MW. Mechanism of inhibition of tannic acid and related compounds on the growth of intestinal bacteria. Food Chem Toxicol 1998;36:1053–60.

Ciesek S, von Hahn T, Colpitts CC, Schang LM, Friesland M, Steinmann J, et al. The green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. Hepatology 2011;54:1947–55.

Coop RL, Kyriazakis IK. Influence of host nutrition on the development and consequences of nematode parasitism in ruminants. Trends Parasitol 2001;17:325–30.

Dey A, De PS. Influence of condensed tannins from Ficus bengalensis leaves on feed utilization. milk production and antioxidant status of crossbred cows. Asian-Australas J Anim Sci 2014;27:342–8.

Di Pasquale G, Ostedgaard L, Vermeer D, Swaim WD, Karp P, Chiorini JA. Bovine AAV transcytosis inhibition by tannic acid results in functional expression of CFTR *in vitro* and altered biodistribution *in vivo*. Gene Ther 2012;19:576–81.

Dollahite JW, Pigeon RF, Camp BJ. The toxicity of gallic acid, pyrogallol, tannic acid, and Quercus havardi in the rabbit. Am J Vet Res 1962;23:1264–7.

Doss A, Mubarack HM, Dhanabalan R. Antibacterial activity of tannins from the leaves of *Solanum trilobatum* Linn. Indian J Sci Technol 2009;2:41–3.

Dschaak CM, Williams CM, Holt MS, Eun J-S, Youn AJ, Min BR. Effects of supplementing condensed tannin extract on intake, digestion, ruminal fermentation, and milk production of lactating dairy cows. J Dairy Sci 2011;94:2508–19.

Dutot M, Fagon R, Hemon M, Rat P. Antioxidant, anti-inflammatory, and anti-senescence activities of a phlorotannin-rich natural extract from brown seaweed *Ascophyllum nodosum*. Appl Biochem Biotech 2012;167(8):2234–40.

Dutta N, Dubey M, Banerjee PS, Pattanaik AK, Sharma K, Kumar P, et al. Effect of supplementing tanniferous tree leaves mixture on immune response and GI nematodes in kids. Livest Res Rural Dev 2012;24(2).

Ebadi MR, Pourreza J, Jamalian J, Edriss MA. Amino acid content and availability in low, medium and high tannin sorghum grain for poultry. Int J Poult Sci 2005;4(1).

Ebrahim R, Liang JB, Jahromi MF, Shokryazdan P, Ebrahimi M, Chen WL, et al. Effects of tannic acid on performance and fatty acid composition of breast muscle in broiler chickens under heat stress. Ital J Anim Sci 2015;14(4):572–7.

Eom SH, Moon SY, Lee DS, Kim HJ, Park K, Lee EW, et al. *In vitro* antiviral activity of dieckol and phlorofucofuroeckol-a isolated from edible brown alga *Eisenia bicyclis* against murine norovirus. Algae 2015;30(3):241–6. 2015.

Farahat MH, Abdallah FM, Ali HA, Hernandez-Santana A. Effect of dietary supplementation of grape seed extract on the growth performance, lipid profile, antioxidant status and immune response of broiler chickens. Animal 2017;11(5):771–7.

Frutos P, Hervás G, Giráldez FJ, Mantecón AR. Review. Tannins and ruminant nutrition. J Biol Chem 2004;2(2):20882–8.

Funatogawa K, Hayashi S, Shimomura H, Yoshida T, Hatano T, Ito H, et al. Antibacterial activity of hydrolyzable tannins derived from medicinal plants against *Helicobacter pylori*. Microbiol Immunol 2004;48:251–61.

Gambacorta L, Pinton P, Avantaggiato G, Oswald IP, Solfrizzo M. Grape pomace, an agricultural byproduct reducing mycotoxin absorption: *in vivo* assessment in pig using urinary biomarkers. J Agri Food Chem 2016;64(35):6762–71.

Gonçalves C, Dinis T, Batista MT. Antioxidant properties of proanthocyanidins of *Uncaria tomentosa* bark decoction: a mechanism for anti-inflammatory activity. Phytochemistry 2005;66:89–98.

Hagerman AE, Riedl KM, Jones GA, Sovik KN, Ritchard NT, Hartzfeld PW, et al. High molecular weight plant polyphenolics (tannins) as biological antioxidants. J Agric Food Chem 1998;46:1887–92.

Haslam E. Plant polyphenols. Vegetable tannins revisited. Cambridge: Cambridge University Press; 1989.

Heckendorn F, Häing DA, Maurer V, Senn M, Hertzberg H. Individual administration of three tanniferous forage plants to lambs artificially infected with *Haemonchus contortus* and Cooperia curticei. Vet Parasitol 2007;146:123–34.

Herbert RB. The biosynthesis of secondary metabolites. London: Chapman and Hall; 1989.

Ho KY, Huang JS, Tsai CC, Lin TC, Hsu YF, Lin CC. Antioxidant activity of tannin component from *Vaccinium vitis-idaea* L. J Pharm Pharmacol 1999;51:1075–8.

Hodnick WF, Milosavljevic EB, Nelson JH, Pardini RS. Electrochemistry of flavonoids. Biochem Pharmacol 1988;37:2607–11.

Hoste H, Jackson F, Athanasiadou S, Thamsborg S, Hoskin SO. The effects of tannin-rich plants on parasitic nematodes in ruminants. Trends Parasitol 2006;32:253–61.

Hoste HC, Martinez-Ortiz-De-Montellano F, Manolaraki S, Brunet N, Ojeda-Robertos I, Fourquaux JF, et al. Direct and indirect effects of bioactive tannin-rich tropical and temperate legumes against nematode infections. Vet Parasitol 2012;186:18–27.

Hollman PCH, Katan MB. Dietary flavonoids: intake, health effects and bioavailability. Food Chem Toxicol 1999;37(9–10):937–42.
Huang QQ, Jin L, Xu Z, Barbieria LR, Acharyaa S, Hu TM, et al. Effects of purple prairie clover (*Dalea purpurea* Vent) on feed intake, nutrient digestibility and faecal shedding of *Escherichia coli* O157: H7 in lambs. Anim Feed Sci Technol 2015;207. 51-1.
Huang QQ, Hu TM, Xu Z, Jin L, McAllister TA, Acharyaa S, et al. Structural composition and protein precipitation capacity of condensed tannins from purple prairie clover (*Dalea purpurea* Vent.). In: ASAS-CSAS joint annual meeting. July 8–12, 2017; 2017 [Baltimore, ML, US].
Ikigai H, Nakae T, Hara Y, Shimamura T. Bactericidal catechins damage the lipid bilayer. Biochim Biophys Acta 1993;1147:132–6.
Iji PA, Khumalo K, Slippers S, Gous RM. Intestinal function and body growth of broiler chickens on maize-based diets supplemented with mimosa tannins and a microbial enzyme. J Sci Food Agri 2004;84:1451–8.
Jamroz D, Wiliczkiewicz A, Skorupińska J, Orda J, Kuryszko J, Tschirch H. Effect of sweet chestnut tannin (SCT) on the performance, microbial status of intestine and histological characteristics of intestine wall in chickens. Brit Poult Sci 2009;50:687–99.
Jin L, Wang Y, Iwaasa AD, Xu Z, Li Y, Schellenberg MP, et al. Purple prairie clover (*Dalea purpurea* Vent) reduces fecal shedding of *Escherichia coli* in pastured cattle. J Food Prot 2015;78:1434–41.
Juhnke J, Miller J, Hall JO, Provenza FD, Villalba JJ. Preference for condensed tannins by sheep in response to challenge infection with Haemonchus contortus. Vet Parasitol 2012;188(1–2):104–14.
Karadeniz F, Kang KH, Park JW, Park SJ, Kim SK. Anti-hiv-1 activity of phlorotannin derivative 8,4‴-dieckol from Korean brown alga ecklonia cava. Biosci Biotechnol Biochem 2014;78(7):1151–8.
Kheng TY. Changes in tannin concentration of rastali banana (*Musa AAB rastali*) during growth and development. Trans Malays Soc Plant Physiol 2010:S237.
Kim EB, Kwak JH. Antiviral phlorotannin from Eisenia bicyclis against human papilloma virus in vitro. Planta Med 2015;81(16).
Kubena LF, Byrd JA, Young CR, Corrier DE. Effects of tannic acid on cecal volatile fatty acids and susceptibility to *Salmonella typhimurium* colonization in broiler chicks. Poult Sci 2001;80(9):1293–8.
Kwon HJ, Ryu YB, Kim YM, Song N, Kim CY, Rho MC, et al. *In vitro* antiviral activity of phlorotannins isolated from ecklonia cava, against porcine epidemic diarrhea coronavirus infection and hemagglutination. Bioorgan Med Chem 2013;21(15): 4706–13.
Lee JH, Vanguru M, Kannan G, Moore DA, Terrill TH, Kouakou B. Influence of dietary condensed tannins from Sericea lespedeza on bacterial loads in gastrointestinal tracts of meat goats. Livest Sci 2009a;126(1):314–7.
Lee SH, Shinde PL, Choi JY, Kwon IK, Lee JK, Pak SI, et al. Effects of tannic acid supplementation on growth performance, blood hematology, iron status and faecal microflora in weanling pigs. Livest Sci 2010;131(2):281–6.
Lee SH, Shinde PL, Choi JY, Kwon IK, Lee JK, Pak SI, et al. Effects of tannic acid added to diets containing low level of iron on performance, blood hematology, iron status and fecal microflora in weanling pigs. J Anim Sci Technol 2009b;51(6): 503–10.
Li Y, Iwaasaa D, Wang Y, Jin L, Han G, Zhao M. Condensed tannins concentration of selected prairie legume forages as affected by phenological stages during two consecutive growth seasons in western Canada. Can J Plant Sci 2014;94:817–26.
Li YG, Tanner G, Larkin P. The DMACA–HCl protocol and the threshold proanthocyanidin content for bloat safety in forage legumes. J Sci Food Agric 1996;70: 89–101.
Lin CC, Hsu YF, Lin TC. Antioxidant and free radical scavenging effects of the tannins of *Terminalia catappa* L. Anticancer Res 2001;21:237–43.
Lisonbee LD, Villalba JJ, Provenza FD, Hall JO. Tannins and self-medication: implications for sustainable parasite control in herbivores. Behav Process 2009;82: 184–9.
Liu C, Cai D, Zhang L, Tang W, Yan R, Guo H, et al. Identification of hydrolyzable tannins (punicalagin, punicalin and geraniin) as novel inhibitors of hepatitis b virus covalently closed circular DNA. Antivir Res 2016;134:97.
Liu HW, Gai F, Gasco L, Brugiapaglia A, Lussiana C, Guo KJ, et al. Effects of chestnut tannins on carcass characteristics, meat quality, lipid oxidation and fatty acid composition of rabbits. Meat Sci 2009;83:678–83.
Liu JB, Ding YS, Zhang Y, Chen JB, Cui BS, Bai JY, et al. Anti-inflammatory hydrolyzable tannins from myricaria bracteata. J Nat Prod 2015a;78(5):1015–25.
Liu S, Chen R, Hagedorn CH. Tannic acid inhibits hepatitis c virus entry into huh7.5 cells. Plos One 2015b;10(7), e0131358.
Liu XL, Hao YQ, Jin L, Xu ZJ, McAllister TA, Wang Y. Anti-*Escherichia coli* O157: H7 properties of purple prairie clover and sainfoin condensed tannins. Molecules 2013;18:2183–99.
López-Andrés P, Luciano G, Vasta V, Gibson TM, Biondi L, Priolo A, et al. Dietary quebracho tannins are not absorbed, but increase the antioxidant capacity of liver and plasma in sheep. Br J Nutr 2013;14:1–8.
Luciano G, Vasta V, Monahan FJ, López-Andrés P, Biondi L, Lanza M, et al. Antioxidant status, colour stability and myoglobin resistance to oxidation of longissimus dorsi muscle from lambs fed a tannin-containing diet. Food Chem 2011;124:1036–42.
Luciano G, Monahan FJ, Vasta V, Biondi L, Lanza M, Priolo A, et al. Dietary tannins improve lamb meat color stability. Meat Sci 2009;81:120–5.
Lüder UH, Clayton MN. Induction of phlorotannins in the brown macroalga Ecklonia radiata (*Laminariales, Phaeophyta*) in response to simulated herbivory, the first microscopic study. Planta 2004;218:928–37.
Maertens L, Štruklec M. Technical note: preliminary results with a tannin extract on the performance and mortality of growing rabbits in an enteropathy infected environment. World Rabbit Sci 2006;14:189–92.
Mansoori B. Absorption capacity of chicken intestine for D-xylose in response to graded concentrations of tannic acid. Anim Feed Sci Technol 2009;151: 167–71.
Mansoori B, Rogiewicz A, Slominski BA. The effect of canola meal tannins on the intestinal absorption capacity of broilers using a d-xylose test. J Anim Physiol Anim Nutr 2015;99(6):1084–93.
Marshall TA, Roberts RJ. *In vitro* and *in vivo* assessment of lipid peroxidation of infant nutrient preparations: effect of nutrition on oxygen toxicity. J Am Coll Nutr 1990;9:190–9.
Marzo F, Tosar A, Santidrian S. Effect of tannic acid on the immune response of growing chickens. J Anim Sci 1990;40:1189–97.
Mcallister TA, Martinez T, Bae HD, Muir AD, Yanke LJ, Jones GA. Characterization of condensed tannins purified from legume forages: chromophore production, protein precipitation, and inhibitory effects on cellulose digestion. J Chem Ecol 2005;31(9):2049.
Mcleod MN. Plant tannins-Their role in forage quality. Nutr Abstr Rev 1974;44(44): 803–12.
McSweeney CS, Palmer B, McNeill DM, Krause DO. Microbial interactions with tannins: nutritional consequences for ruminants. Anim Feed Sci Technol 2001;91:83–93.
Mercurio MD, Smith PA. Tannin quantification in red grapes and wine: comparison of polysaccharide- and protein-based tannin precipitation techniques and their ability to model wine astringency. J Agri Food Chem 2008;56(14):5528.
Mertz C, Cheynier V, Günata Z, Brat P. Analysis of phenolic compounds in two blackberry species (*rubus glaucus* and *rubus adenotrichus*) by high-performance liquid chromatography with diode array detection and electrospray ion trap mass spectrometry. J Agric Food Chem 2007;55(21):8616–24.
Min BR, Hart SP. Tannins for suppression of internal parasites. J Anim Sci 2003;81: E102–9.
Min BR, Barry TN, Attwood GT, Mcnabb WC. The effect of condensed tannins on the nutrition and health of ruminants fed fresh temperate forages: a review. Anim Feed Sci Technol 2003;106(s1–4):3–19.
Min BR, Hart SP, Miller D, Tomita GM, Loetz E, Sahlu T. The effect of grazing forage containing condensed tannins on gastro-intestinal parasite infection and milk composition in angora does. Vet Parasitol 2005;130:105–13.
Min BR, Hernandez K, Pinchak WE, Anderson RC, Miller JE, Valencia E. Effects of plant tannin extracts supplementation on animal performance and gastrointestinal parasites infestation in steers grazing winter wheat. Open J Anim Sci 2015;5:343–50.
Min BR, Pinchak W, Anderson RC, Callaway TR. Effect of tannins on the *in vitro* growth of *Escherichia coli* O157: H7 and *in vivo* growth of generic *Escherichia coli* excreted from steers. J Food Prot 2007;70:543–50.
Miller LH, Su X. Artemisinin: discovery from the Chinese herbal garden. Cell 2011;146(6):855–8.
Molan AL, Duncan AJ, Barry TN, Mcnabb WC. Effects of condensed tannins and crude sesquiterpene lactones extracted from chicory on the motility of larvae of deer lungworm and gastrointestinal nematodes. Parasitol Int 2003;52:209–18.
Molan AL, Hoskin SO, Barry TN, McNabb WC. Effect of condensed tannins extracted from four forages on the viability of the larvae of deer lungworms and gastrointestinal nematodes. Vet Rec 2000a;147:44–8.
Molan AL, Waghorn GC, Min BM, McNabb WC. The effect of condensed tannins from seven herbages on *Trichostrongylus colubriformis* larval migration *in vitro*. Folia Parasitol 2000b;47:39–44.
Molan AL, Sivakumaran S, Spencer PA, Meagher LP. Green tea flavan-3-ols and oligomeric proanthocyanidins inhibit the motility of infective larvae of *Teladorsagia circumcincta* and *Trichostrongylus colubriformis in vitro*. Res Vet Sci 2004;77(3):239–43.
Molan AL, Warghorn GC, McNabb WC. Effect of condensed tannins on egg hatching and larval development of *Trichostrongylus colubriformis in vitro*. Vet Rec 2002;150:65–9.
Mota ML, Thomas G, Barbosa Filho JM. Anti-inflammatory actions of tannins isolated from the bark of *Anacardium occidentale* L. J Ethnopharmacol 1985;13: 289–300.
Mueller-Harvey I. Unravelling the conundrum of tannins in animal nutrition and health. J Sci Food Agri 2006;86(13):2010–37.
Murdiati TB, McSweeney CS, Campbell RSF, Stoltz DS. Prevention of hydrolysable tannin toxicity in goats fed *Clidemia hirta* by calcium hydroxide supplementation. J Appl Toxicol 1990;10:325–31.
Nonaka GI, Sakai R, Nishioka I. Hydrolysable tannins and proanthocyanidins from green tea. Phytochemistry 1984;23(8):1753–5.
Okuda T, Mori K, Hatano T. Relationship of the structures of tannins to the binding activities with hemoglobin and methylene blue. Chem Pharm Bull 1985;33: 1424–33.
Paolini V, Frayssines A, De LFF, Dorchies P, Hoste H. Effects of condensed tannins on established populations and on incoming larvae of *Trichostrongylus colubriformis* and *Teladorsagia circumcincta* in goats. Vet Res 2003;34:331–9.
Park M, Cho H, Jung H, Lee H, Hwang KT. Antioxidant and anti-inflammatory activities of tannin fraction of the extract from black raspberry seeds compared to grape seeds. J Food Biochem 2014;38(3):259–70.
Parys AV, Boyen F, Dewulf J, Haesebrouck F, Pasmans F. The use of tannins to control *Salmonella typhimurium* infections in pigs. Zoonoses Public Health 2010;57(6): 423–8.

Pathak AK, Dutta N, Banerjee PS, Goswami TK, Sharma K. Effect of condensed tannins supplementation through leaf meal mixture on voluntary feed intake, immune response and worm burden in *Haemonchus contortus* infected sheep. J Parasit Dis 2016;40:100.

Patra AK, Saxena J. Exploitation of dietary tannins to improve rumen metabolism and ruminant nutrition. J Sci Food Agri 2011;91(1):24–37.

Peng K, Shirley DC, Xu Z, Huang QQ, Mcallister TA, Chaves AV, et al. Effect of purple prairie clover (*Dalea purpurea*, vent.) hay and its condensed tannins on growth performance, wool growth, nutrient digestibility, blood metabolites and ruminal fermentation in lambs fed total mixed rations. Anim Feed Sci Technol 2016;222:100–10.

Pinna W, Nieddu G, Moniello G, Cappai MG. Vegetable and animal food sorts found inthe gastric content of Sardinian Wild Boar (*Sus scrofa meridionalis*). J Anim Physiol Anim Nutr 2007;91:252–5.

Prieur C, Rigaud J, Cheynier V, Moutounet M. Oligomeric and polymeric procyanidins from grape seeds. Phytochemistry 1994;36(3):781–4.

Ragan MA, Glombitza KW. Phlorotannins, brown algal polyphenols. Prog Phycol Res 1986;4:129–241.

Redondo LM, Chacana PA, Dominguez JE, Fernandez Miyakawa ME. Perspectives in the use of tannins as alternative to antimicrobial growth promoter factors in poultry. Front Microbiol 2014;5:118.

Rezar V, Salobir J. Effects of tannin-rich sweet chestnut (*Castanea sativa* mill.) wood extract supplementation on nutrient utilisation and excreta dry matter content in broiler chickens. Eur Poult Sci 2014;78.

Ricci A, Olejar KJ, Parpinello GP, Mattioli AU, Teslić N, Kilmartin PA, et al. Antioxidant activity of commercial food grade tannins exemplified in a wine model. Food Addit Contam A 2016;33(12):1761–74.

Rice-Evans CA, Miller NJ, Bolwell PG, Bramley PM, Pridham JB. The relative antioxidant activities of plant-derived polyphenolic flavonoids. Free Radic Res 1995;22:375–83.

Rice-Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Bio Med 1996;20(7):933–56.

Riedl KM, Hagerman E. Tannin–protein complexes as radical scavengers and radical skins. J Agric Food Chem 2001;49:4917–23.

Rivera-Méndez C, Plascencia A, Torrentera N, Zinn RA. Effect of level and source of supplemental tannin on growth performance of steers during the late finishing phase. J Appl Anim Res 2017;45(1):199–203.

Ryu YB, Jeong HJ, Yoon SY, Park JY, Kim YM, Park SJ, et al. Influenza virus neuraminidase inhibitory activity of phlorotannins from the edible brown alga ecklonia cava. J Agri Food Chem 2011;59(12):6467–73.

Sakanaka S, Skim M, Taniguchi M, Yamamoto T. Antibacterial substances in Japanese green tea extract against Streptococcus mutans, a cariogenic bacterium. Agric Biol Chem 1989;53:2307–11.

Salunkhe DK, Jadhav SJ, Kadam SS, Chavan JK. Chemical, biochemical, and biological significance of polyphenols in cereals and legumes. Crit Rev Food Sci Nutr 1982;17(3):277–305.

Scalbert A. Antimicrobial properties of tannins. Phytochemistry 1991;30:3875–83.

Scalbert A, Manach C, Morand C, Rémésy C, Jiménez L. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr 2005;45(4):287–306.

Schiavone A, Guo K, Tassone S, Gasco L, Hernandez E, Denti R, et al. Effects of a natural extract of chestnut wood on digestibility, performance traits, and nitrogen balance of broiler chicks. Poult Sci 2008;87(3):521–7.

Shibata T, Kawaguchi S, Hama Y, Inagaki M, Yamaguchi K, Nakamura T. Local and chemical distribution of phlorotannins in brown algae. J Appl Phycol 2004;16:291–6.

Smith AH, Mackie RI. Effect of condensed tannins on bacterial diversity and metabolic activity in the rat gastrointestinal tract. Appl Environ Microbiol 2004;70:1104–15.

Smith T, Mlambo V, Sikosana JLN, Maphosa V, Mueller-Harvey I, Owen E. *Dichrostachys cinerea* and *Acacia nilotica* fruits as dry season feed supplements for goats in a semi-arid environment—summary results from a DFID funded project in Zimbabwe. Anim Feed Sci Technol 2005;122:149–57.

Sottie ET, Acharya SN, McAllister T, Thomas J, Wang Y, Iwaasa I. Alfalfa pasture bloat can be eliminated by intermixing with newly-developed sainfoin population. Agron J 2014;106:1470–8.

Starčević K, Krstulović L, Brozić D, Maurić M, Stojević Z, Mikulec Ž, et al. Production performance, meat composition and oxidative susceptibility in broiler chicken fed with different phenolic compounds. J Sci Food Agri 2015;95(6):1172–8.

Štukelj M, Valenčak Z, Krsnik M, Nemec-Svete A. The effect of the combination of acids and tannin in diet on the performance and selected biochemical, haematological and antioxidant enzyme parameters in grower pigs. Acta Vet Scan 2010;52:1–8.

Souza SMC, Aquino LCM, ACM Jr , Bandeira MAM, Nobre MEP, Viana GSB. Antiinflammatory and antiulcer properties of tannins from *Myracrodruon urundeuva* allemão (anacardiaceae) in rodents. Phytother Res 2007;21(3):220–5.

Sugiura Y, Tanaka R, Katsuzaki H, Imai K, Matsushita T. The anti-inflammatory effects of phlorotannins from eisenia arborea, on mouse ear edema by inflammatory inducers. J Funct Foods 2013;5(4):2019–23.

Tan GT, Pezzuto JM, Kinghorn AD, Hughes SH. Evaluation of natural products as inhibitors of human immunodeficiency virus type 1 (hiv-1) reverse transcriptase. J Nat Prod 1991;54(1):143.

Targett NM, Arnold TM. Predicting the effects of brown algal phlorotannins on marine herbivores in tropical and temperate oceans. J Phycol 1998;34:195–205.

Terra X, Valls J, Vitrac X, Mérrillon JM, Arola L, Ardèvol A, et al. Grape-seed procyanidins act as antiinflammatory agents in endotoxin-stimulated RAW 264.7 macrophages by inhibiting NFkB signaling pathway. J Agric Food Chem 2007;55:4357–65.

Terrill TH, Rowan AM, Douglas GB, Barry TN. Determination of extractable and bound condensed tannin concentrations in forage plants, protein concentrate meals and cereal grains. J Sci Food Agri 1992;58(3):321–9.

Tosi G, Massi P, Antongiovanni M, Buccioni A, Minieri S, Marenchino L, et al. Efficacy test of a hydrolysable tannin extract against necrotic enteritis in challenged broiler chickens. Ital J Anim Sci 2013;12:123–32.

Tzamaloukas O, Athanasiadou S, Kyriazakis I, Huntley J. The effect of chicory (*Cichorium intybus*) and sulla (*Hedysarum coronarium*) on larval development and mucosal cell responses of growing lambs challenged with *Teladorsagia circumcincta*. Parasitology 2006;132:419–26.

Uchiumi F, Hatano T, Ito H, Yoshida T, Tanuma S. Transcriptional suppression of the HIV promoter by natural compounds. Antivir Res 2003;58(1):89–98.

Ueda K, Kawabata R, Irie T, Nakai Y, Tohya Y, Sakaguchi T. Inactivation of pathogenic viruses by plant-derived tannins: strong effects of extracts from persimmon (*Diospyros kaki*) on a broad range of viruses. PLoS One 2013;8(1):e55343.

Van Soest PJ. Nutritional ecology of the ruminant, vol. 44. Cornell University; 1982. p. 2552–61 (11).

Viveros A, Chamorro S, Pizarro M, Arija I, Centeno C, Brenes A. Effects of dietary polyphenol-rich grape products on intestinal microflora and gut morphology in broiler chicks. Poult Sci 2011;90(3):566–78.

Waghorn G. Beneficial and detrimental effects of dietary condensed tannins for sustainable sheep and goat production—progress and challenges. Anim Feed Sci Tech 2008;147(3):116–39.

Wang ML, Suo X, Gu JH, Zhang WW, Fang Q, Wang X. Influence of grape seed proanthocyanidin extract in broiler chickens: effect on chicken coccidiosis and antioxidant status. Poult Sci 2008;87(11):2273–80.

Wang Y, Berg BP, Barbieri LR, Veira DM, Mcallister TA. Feed intake, ruminal fermentation, and development of bloat in steers grazing pastures of alfalfa or mixed alfalfa-sainfoin. Can J Anim Sci 2006;86(3):383–92.

Wang Y, Jin L, Ominski KH, He M, Xu Z, Krause DO, et al. Screening of condensed tannins from canadian prairie forages for anti-*Escherichia coli* O157:H7 with an emphasis on purple prairie clover (*Dalea purpurea* vent). J Food Prot 2013;76(4):560–7.

Wang Y, Majak W, Mcallister TA. Frothy bloat in ruminants: cause, occurrence, and mitigation strategies. Anim Feed Sci Technol 2012;172(1–2):103–14.

Wang Y, McAllister TA. Brown algae as feed additive: nutritional and health impacts on ruminant animals – a review. In: Borgearo SR, editor. Animal feed: types, nutrition, and safety. Nova Science Publishers; 2011. p. 1–32.

Wang Y, Mcallister TA, Acharya S. Condensed tannins in sainfoin: composition, concentration, and effects on nutritive and feeding value of sainfoin forage. Crop Sci 2015;55(1):13–22.

Wang Y, McAllister TA, Xu Z, Cheng KJ. The effects of proanthocyanidins, dehusking and depericarping on the digestion of barley grain by ruminants. J Sci Food Agri 1999;79:929–38.

Wang Y, Waghorn GC, Barry TN, Shelton ID. The effect of condensed tannins in *Lotus corniculatus* on plasma metabolism of methionine, cystine and inorganic sulphate by sheep. Brit J Nutr 1994;72(6):923–5.

Wang Y, Waghorn GC, Mcnabb WC, Barry TN, Hedley MJ, Shelton ID. Effects of condensed tannins in *Lotus corniculatus* upon the digestion of methionine and cysteine in the small intestine of sheep. J Agr Sci 1996;127:413–21.

Wang Y, Xu Z, Bach SJ, McAllister TA. Sensitivity of *Escherichia coli* O157:H7 to seaweed (*Ascophyllum nodosum*) phlorotannins and terrestrial tannins. Asian-Aust J Anim Sci 2009;22:238–45.

Wijesinghe WAJP, Ginnae A, Wonwoo L, Kang MC, Euna K, Youjin J. Anti-inflammatory activity of phlorotannin-rich fermented ecklonia cava processing by-product extract in lipopolysaccharide-stimulated raw 264.7 macrophages. J Appl Phycol 2013;25(4):1207–13.

Wina E, Tangendjaja B, Susana IWR. Effects of chopping, and soaking in water, hydrochloric acidic and calcium hydroxide solutions on the nutritional value of *Acacia villosa* for goats. Anim Feed Sci Technol 2005;122:79–92.

Xu H, Wan MH, But P, Foo L. Inhibitory activity of flavonoids and tannins against hiv-1 protease. Biol Pharm Bull 2000;23(9):1072–6.

Yan L, Kim IH. Effect of dietary grape pomace fermented by *saccharomyces boulardii* on the growth performance, nutrient digestibility and meat quality in finishing pigs. Asian-Australas J Anim Sci 2011;24(12):2806–13.

Yang C, Chowdhury MA, Huo Y, Gong J. Phytogenic compounds as alternatives to in-feed antibiotics: potentials and challenges in application. Pathogens 2015;4(1):137–56.

Yang Y, Xiu J, Liu J, Zhang L, Li X, Xu Y, et al. Chebulagic acid, a hydrolyzable tannin, exhibited antiviral activity *in vitro* and *in vivo* against human enterovirus 71. Int J Mol Sci 2013;14(5):9618.

Zhang XF, Dai YC, Zhong W, Tan M, Lv ZP, Zhou YC, et al. Tannic acid inhibited norovirus binding to HBGA receptors, a study of 50 Chinese medicinal herbs. Bioorg Med Chem 2012;20:1616–23.

Zoccarato I, Gasco L, Schiavone A, Guo K, Barge P, Rotolo L, et al. Effect of extract of chestnut wood inclusion (ENC) in normal and low protein aminoacid supplemented diets on heavy broiler rabbits. In: Proceedings of the 9th world rabbit congress; 2008. p. 689–93. Verona.

Zotte AD, Cossu ME. Dietary inclusion of tannin extract from red quebracho trees (*Schinopsis* spp.) in the rabbit meat production. Ital J Anim Sci 2009;8(2):784–6.