



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.

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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 phytochemicals) 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, gallo catechin 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, Isofufhalols, Echole, Fucole, Fufhalols, 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 extra-cellular 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 (McCallister 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, anti-microbial 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; Bansa 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 (gallo catechin) 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 (*Athanasiaadou* 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 (Athanasidou 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

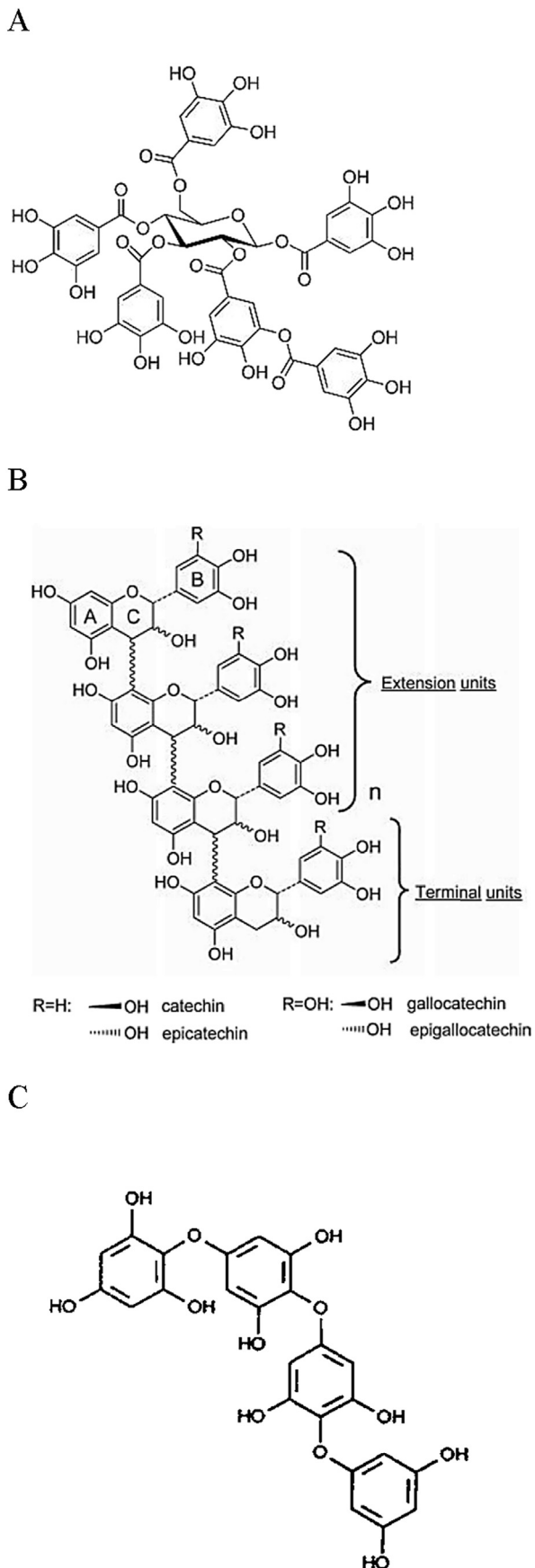


Fig. 1. Model structures of (A) hydrolyzable tannins, (B) condensed tannins and (C) phlorotannins.

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 studied 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

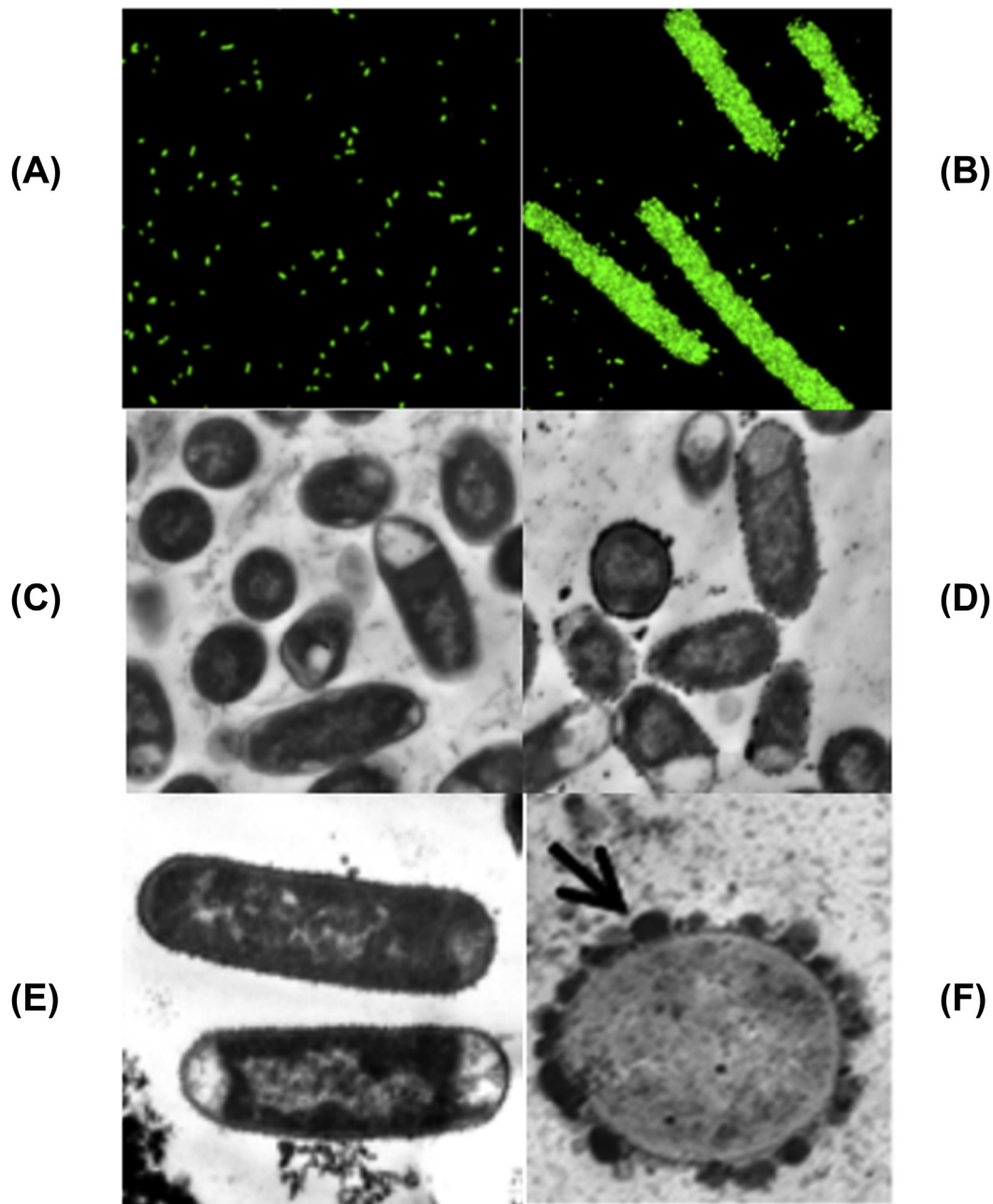


Fig. 2. Aggregation of *Escherichia coli* (strain 25922) cell incubated for 10 h with (A) 0 (Control) or (B) 200 $\mu\text{g}/\text{mL}$ of condensed tannins of purple prairie clover (*Dalea purpurea* Vent.), and transmission electron micrographs of *E. coli* O157:H7 strain 3081 incubated for 24 h with (C) 0 or 50 $\mu\text{g}/\text{mL}$ 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

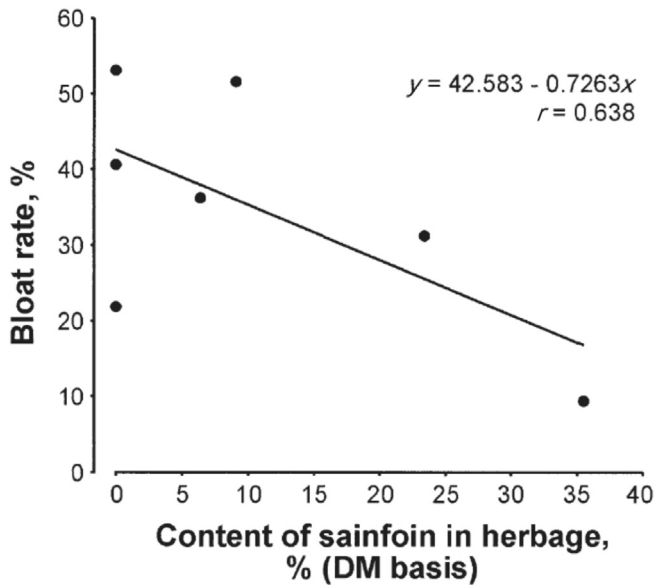


Fig. 3. Regression of bloat rate and proportion of sainfoin in herbage mass determined for beef steers ($n = 12$) grazing forage re-growth in 1999 and 2000 (adapted from Wang et al. (2006)).

(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-borne 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 (Schiaivone 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
<i>Ascophyllum nodosum</i> extract	Phlorotannins (PT)	Feedlot cattle	Grain based diet	0, 10 or 20 g/kg diet, 14 days prior to slaughtering	Reduced fecal and hide <i>E. coli</i> and <i>E. coli</i> O157:H7	Behrends et al. (2000)
<i>A. nodosum</i> meal	PT	Cattle	Grain based diet	20 g/kg DM	Reduced both fecal and hide <i>E. coli</i> O157:H7 and <i>Salmonella</i>	Barham et al. (2001)
<i>A. nodosum</i> meal	PT	Feedlot cattle	Corn-based diet	20 g/kg diet, 14 day pre-slaughtering	Reduced <i>E. coli</i> O157:H7 prevalence on hide swabs and in fecal samples	Braden et al. (2004)
<i>A. nodosum</i> meal	PT	<i>E. coli</i> O157:H7 challenged cattle	Barley based concentrate diet	10 or 20 g/kg diet, up to 14 days	Reduced fecal shedding of <i>E. coli</i> O157:H7	Bach et al. (2008)
Purple prairie clover	Condensed tannins (CT)	<i>E. coli</i> O157:H7 challenged lamb	Fresh forage	36 g/kg DM ECT	Reduced <i>E. coli</i> O157:H7 fecal shedding	Huang et al. (2015)
<i>Sericea lespedeza</i>	CT	Goat	Hay	13.5 g/kg DM ECT	No effect on fecal <i>E. coli</i>	Lee et al. (2009a,b)
Chestnut	Hydrolyzable tannins (HT)	Cattle	Hay	15 g/day	Reduced fecal <i>E. coli</i>	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 <i>E. coli</i> 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 iso-valeric 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). Stukelj 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 chestnut 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 Struklec, 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, Clostridiales, *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 <i>E. coli</i>	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 <i>Salmonella</i> ; 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 <i>Clostridium perfringens</i> (<i>Eimeria tenella</i> , <i>Eimeria acervulina</i> , <i>Eimeria maxima</i>) 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, Clostridiales, 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 <i>E. coli</i> , Lactobacillus, Enterococcus, and Clostridium in the cecal digesta	Viveros et al. (2011)
Grape seed extract	CT	<i>Eimeria tenella</i> challenged broiler chickens	5, 10, 20, 40, and 80 mg/kg diet	Decreased mortality and increased weight gain after the <i>E. tenella</i> 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 <i>Newcastle</i> 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)
<i>Saccharomyces boulardii</i> 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 <i>Malaysia</i> more effective than red grape pomace <i>Primitivo</i>	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 <i>Lactobacillus</i> , <i>Enterococcus</i> and decreased the counts of <i>Clostridium</i> in the ileal content; increased populations of <i>E. coli</i> , <i>Lactobacillus</i> , <i>Enterococcus</i> , and <i>Clostridium</i> 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, <i>Clostridium</i> spp. and coliforms but increased <i>Bifidobacterium</i> spp. and <i>Lactobacillus</i> 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 <i>Salmonella</i> cecal culture-positive chicks or in the numbers of <i>Salmonella typhimurium</i> 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 <i>E. coli</i> 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 (<i>Schinopsis lorentzii</i>)	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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