Animal Feed Science and Technology 264 (2020) 114469

Contents lists available at ScienceDirect

Animal Feed Science and Technology

journal homepage: www.elsevier.com/locate/anifeedsci

Review article

Plant secondary metabolites as feed additives in calves for antimicrobial stewardship

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ARTICLE INFO

Keywords:
Calves
Feed additives
Antimicrobial
Herbs
Plant extracts
Plant secondary metabolites

ABSTRACT

Irrational usage of antibiotic feed additives in livestock industry, especially as growth promoters, has become a global challenge due to the unintended zoonotic impact through resistance transfer. Herbal plant extracts or their secondary metabolites with antimicrobial properties may possess similar effects of various antibiotic feed additives in impeding the pathogenic microbial growth and enhancing the health, growth, and production performance. Majority of the calf-plant extract associated research works were primarily geared towards phenolic compounds and essential oils, with a few related to terpenes, saponins, tannins, flavonoids, organic acids, complex carbohydrates, and non-protein amino acids. The plant secondary metabolites possess diverse antimicrobial mechanisms, including cell membrane disruption, enzyme inhibition, substrate deprivation, and prevention of bacterial colonization, to name a few. Further, the unification of different levels and types of plant metabolites before supplementing to calves renders synergistic effects, which aids in several beneficial responses such as increased bioavailability, improved efficiency, and reduced undesirable effects and effective dosage. Nevertheless, the employment of herbal extracts or plant metabolites as antimicrobial feed additives to calves retain many challenges regarding the dosages, levels, adaptation lengths, herbal or herb-drug interactions, analytical methods, and public health safety. The present review focuses on assembling existing data on the plant-based antimicrobial components, individual secondary plant metabolites or plant extracts, which are already in use or having the efficacy in benefitting calves on supplementation.

Abbreviations: ADG, average daily gain; BW, bodyweight; BWG, bodyweight gain; CEC, Commission of the European communities; CT, condensed tannins; DM, dry matter; DMI, dry matter intake; DNA, deoxyribonucleic acid; EFSA, European Food Safety Authority; FI, feed intake; FOS, fructo-oligosaccharides; GIT, gastro-intestinal tract; HT, hydrolyzable tannins; IgG, immunoglobulin G; MOS, mannanoligosaccharides; PSM, plant secondary metabolites; TCA, trichloroacetic acid; TVFA, total volatile fatty acids; NH_3-N, ammonia nitrogen; USDA, United States Department of Agriculture; WG, weight gain

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https://doi.org/10.1016/j.anifeedsci.2020.114469
Received 10 August 2018; Received in revised form 27 January 2020; Accepted 4 March 2020
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1. Introduction

Calfhood diseases trigger a significant impact on the frugality of cattle farming activities because of direct losses apart from the long-term effects on the performance (Lorenz et al., 2011). In this regard, calf health could be highlighted as one of the most significant livestock health issues being faced by livestock farmers. Calf mortality is a global challenge that needs to be addressed for sustainable livestock farming. Of the 5% mortality rate in pre-weaned calves, 56% is attributed to digestive problems and scours with remaining caused by respiratory problems (USDA, 2016). The relevant policymakers are involved with implications in preventing the calfhood diseases by supplementing the antimicrobial compounds through diet. Antibiotics have been used at sub-therapeutic levels to encourage the growth and minimize the morbidity and mortality throughout the animals' life cycle. Employing antibiotics as feed additives could be traced back to 1950's (Kertz et al., 2017). However, prolonged application of antibiotic feed additives in livestock sector could cause the continuous adaptation of microbes to the antibiotics, thus generating resistance against antimicrobial agents (Schwarz et al., 2017). Resistance to indispensable antibiotics such as broad-spectrum beta-lactams, aminoglycosides, carbapenems, and fluoroquinolones, is of increasing magnitude among zoonotic pathogens (Zhang et al., 2018). Apropos of the antimicrobial resistance phenomenon, the antibiotic supplementation is worth reevaluating; hence, its usage has been banned in the European Union since January 2006 (Directive 1831/2003/CEE, European Commission, 2003). In this theme, the perspectives in calf nutrition towards antibiotic feed additives have been changing with a shift to the encouraged use of plant secondary metabolites (PSMs) or natural herbal extracts.

Plant secondary metabolites are an exceedingly large group of compounds with small molecular weights, which are meant for protective purposes against insects, microbes, and herbivores, in addition, to adapt to adverse environmental conditions. In nature, these PSM's play important roles as antibacterials, antifungals, antivirals, herbicides, and insecticides (Miguel, 2010); among them, antibacterial activity is one of the greatest notable contributing features for animal agriculture. Plant secondary metabolites are usually considered as anti-nutritional factors for calves and monogastric species. Nevertheless, few investigations have revealed that some of them would beneficially affect the host metabolism and performance when used at appropriate levels. The global herbal products market size has been continuously growing and predicted to reach $111 billion by the end of 2023, with a compound annual growth rate of ~ 7.2% during 2017-2023 (Elghandour et al., 2018). This abrupt hike in herbal market could be taken as a shred of evidence for increasing consumer preference towards plant secondary metabolites as feed additives. The implications pertaining to herbal research in adult ruminants could not be adopted for calves, as younger calves, especially those fed on milk replacer, behave as monogastric species due to the presence of an incompletely formed or non-functional rumen with a well-developed abomasum. As an example, the ionophore antibiotics may show less beneficial effects in young calves compared to adult ruminant species, presumably because of the low microbial population in undeveloped rumen (Akbarian-Tefaghi et al., 2018). Besides the antimicrobial benefits, supplementation of plant extracts or secondary metabolites may deliver flavor to poor quality or low appetence calf starters, which might further enhance the ingesting competence and growth performance (Montoro et al., 2011). Furthermore, few phytonutrients can exert a prebiotic effect in post-weaning calves by escaping the rumen microbial degradation and reaching the small intestine in biologically active form (Wolfswinkel, 2016). The purpose of this review paper is to synthesize an elaborative summary of the published calf-PSM related peer-reviewed papers and discuss their modes of action, different synergic mechanisms, and challenges in dietary supplementation to calves.

2. Plant secondary metabolites as feed additives in calves

Many research works were conducted in relation to the performance-enhancing effects of plant-based antimicrobials for various livestock species and many more have been reviewed for pigs (Liu et al., 2018), poultry (Venkitanarayanan et al., 2013) and other adult livestock species (Mendel et al., 2017); nevertheless, the lowest precedence was given to calves. Since PSMs have been adequately discussed in all species other than calves, the focus of this review will be on the appraisal of PSMs in calves alone. The host-beneficial effects of various PSMs may be mainly contributed by their antimicrobial action. Therefore, a thorough understanding of all the mechanisms of action of different PSMs is necessary to obtain effective outcomes in terms of growth performance, feed efficiency (FE), and welfare of the calves. The principal mechanisms for the antimicrobial action of various PSMs are depicted in Fig. 1. In an elegant review, Cowan et al. (1999) surveyed numerous plants, their secondary metabolites, and susceptible microbes along with their relative toxicity levels; nevertheless, not all of the plants possess the ability to use as feed additives in calves. As per the convenience, the potentiality of various PSMs as feed additives for calves was discussed on an individual basis according to the classification given by Wink (2015).

3. Nitrogen-free secondary metabolites

3.1. Terpenes

Terpenes are a large and diverse class of organic compounds, which can be partitioned into monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes. They are the primary constituents of the essential oils and saponins. Terpenes show lethal or cytotoxic activity against a broad range of microbes, fungi, and even for enveloped viruses. They increase the permeability and fluidity of the membranes, further causing an efflux of metabolites and ions and ultimately leading to cell leakage and microbial death (Wink, 2007). The research concerning the usage of terpene compounds in calves and their results are presented in Table 1.

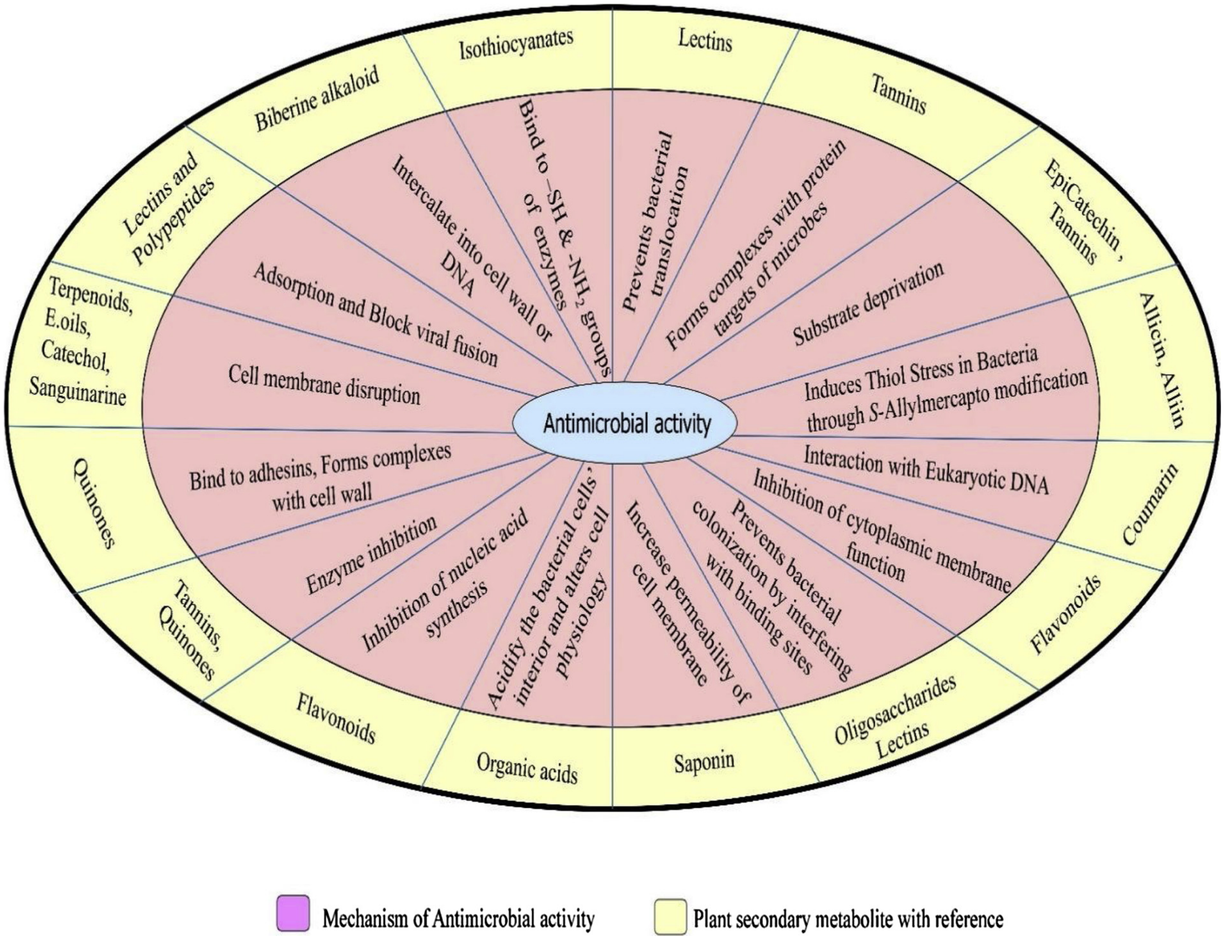

Fig. 1. Mechanisms of Antimicrobial action of various calf-based plant secondary metabolite feed additives.
*Image compiled by using the data from Arabski et al. (2012); Cowan (1999); Dulebohn et al. (2011), Jacob et al. (2008), Krachler and Orth (2013), Luciano et al. (2008); Mitra et al. (2018); Muller et al. (2016); Obiang-Obounou et al. (2011); Vigant et al. (2015); Wang et al. (2016); Xie et al. (2015).

3.1.1. Monoterpenes, sesquiterpenes, and diterpenes

Terpene-based essential oils, generally used as natural insect repellants, perfumes, phytomedicines, and aroma-therapeutic agents, are globally accepted antimicrobial feed additives. These essential oils are more commonly used as taste enhancers or therapeutic agents or aromatherapeutic means rather than feed additives (Wink, 2015).

Though not used as a feed additive, thujone (present in *Tanacetum vulgare* and *Artemisia absinthium*), a monoterpene component is commonly used for deworming in calves because of its ability to alkylate few proteins of neuronal signal transduction (Waller et al., 2001). Further, the plants containing iridoid glucosides, a subclass of monoterpenes, are generally promoted in Ayurvedic medicine to treat various infections. Because of the appetite-stimulating property of iridoid glucosides of Menyanthaceae and Gentianaceae families, they may present a promising role in enhancing calves' dry matter intake (DMI) and growth performance, when supplemented as a feed additive (Mirzaee et al., 2017). Even though the sesquiterpenes and diterpenes possess potent antibacterial activity, their usage as a feed supplement is not suggested because of the lethal effects on host (Wink, 2015).

3.1.2. Triterpenes, steroidal glycosides, and saponins

During recent years, several plant-based hormonally active substances have been promoted for usage in calves under different trade names. They comprise few triterpenes and steroids, which show physical resemblance with hormones; therefore, modulating the hormonal responses in animals. Phytoecdysteroids were proved to possess an inhibitory effect on calf's skin collagenase enzyme, which is involved in aging skin diseases (Nsimba et al., 2008). Further, a detectable quantity of 17-α boldenone component (androgenic steroid) was found in urine samples collected from the veal calves fed an herbal supplemented diet containing phytosterols at 79 or 87.4 mg/100 g (Draisci et al., 2007). The boldenone components possess potent anabolic properties and are extensively used as a supplement for animals' growth and body weight gain (BWG; Cannizzo et al., 2007); however, their usage is prohibited in any livestock species under directives 96/22/EC (CEC, 1996) and 03/74/EC (CEC, 2003) for consumers' health concern. More research has to be conducted on testing the competence of phytosterol rich compounds as alternatives for banned anabolic steroids such as

Table 1
Plant extracts, active components, effect, and calves research of terpene compounds.

Class	Reference	Type of PSM, dosage and period fed	Findings of the Research work
Essential oils	Ahmed et al. (2009)	Herbal mix (garlic, lemonade, and anion juices mixed at 1:0.125:1/liter water) fed at 2.5 g, 5 g, and 7.5 g/Kg diet for 140 days.	Improved nutrient utilization, growth rate, and economical efficiency at 2.5% of the diet. Decreased growth rate equal to that of control at 5% and 7.5% of the diet.
Essential oils	Akbarian-Tefaghi et al. (2018)	A mixture of thyme, celery, and eucalyptus fed at 23 g/kg DM for a period of 70 days.	Improved FE and BWG. Increased molar proportions of acetate and butyrate.
Essential oils	Bampidis et al. (2006)	Calves fed with neomycin or oregano essential oil at 10 mg/kg BW/calf for 37 days.	Fecal score and mortality rates were equal to that of Neomycin.
Essential oils	Mario-Benedeti et al. (2017)	A mixture of Thymol, guaiacol, eugenol, vanilin, salicylaldehyde and limonene fed at 300 mg/kg diet for 75 days.	No effect on BWG and FE during pre-weaning period. Improved FE, reduced fecal score during post-weaning period.
Essential oils	Bittner (2016)	Next enhance (NE) - 300 (contains cinnamaldehyde, garlic, and mineral oil). Trial I – NE-300 at 300 mg/steer/d. Trial II – NE-300 at 0, 75, 150, 225, and 300 mg/steer/d. Trial III – NE-300 at 0, 16.5, 33.1, or 49.6 mg/kg DMI. Trials conducted for entire finishing period.	Trial I – No effect on finishing performance. Trial II – Improved FE linearly with dose. Trial III – No effect on DMI and ADG.
Essential oils	Ebrahimi et al. (2018)	Ajwain oil mixed in milk at 1 or 2 ml/day per calf and thyme oil mixed in milk at 1 or 2 ml/day per calf.	Both sources increased nutrient digestibility and certain hemato-biochemical parameters. No effect on growth performance.
Essential oils	Froehlich (2017)	Stay Strong Essential oil; Altech, Nicholasville, KY (contains garlic, anise, cassia, rosemary, and thyme) fed at 1.25, 2.5, and 3.75 g/calf/feeding for 120 days.	Improved growth, FE, fecal score, and antibody titers.
Essential oils	Jeshari et al. (2016)	Rosemary, shirazi thyme, and squaw mint fed at 300 mg/kg starter diet or distillation residue fed at 50 g/kg starter for 6 months.	Increased feed intake, ADG, and serum insulin concentration.
Essential oils	Kazemi-Bonchenari et al. (2018)	A mixture of thymol, eugenol, vanillin, limonene and guaiacol fed at 1 g/kg starter DM for 80 days.	Improved BWG, growth, and FE.
Essential oils	Meyer et al. (2009)	A mixture of thymol, eugenol, vanilin, guaiacol, and limonene fed at 1 g/calf/d for entire finishing period.	The performance attributes were similar to that of control group.
Essential oils	Rivaroli et al. (2017)	A mixture of oregano, garlic, lemon, rosemary, thyme, eucalyptus, and sweet orange fed at 500 or 1000 mg/kg of DM/calf/day for a period of 120 days.	No effect on DMI, BWG, and carcass characteristics.
Essential oils	Santos et al. (2015)	Active mixture (contains carvacrol, cineole, cinnamaldehyde, and pepper) at 200 mg/kg BW or 400 mg/kg BW for 10 weeks.	No effect on growth performance, fecal scores, intestinal microbes, and ruminal parameters.
Essential oils	Soltan (2009)	A mixture of eucalyptus oil, menthol crystal, mint oil fed at 0, 94, 187, or 281 mg/calf/day for 16 weeks.	In pre-weaning period - No effect of FE and BWG. Improved health score and nutrient digestibility; Decreased diarrheic incidence. In post-weaning period – Improved BWG and FE.
Essential oils	Vakili et al. (2013)	Thyme and cinnamon fed at 5 g/day/calf for 45 days.	No effect on DMI, ADG, FE, plasma metabolites, improved ruminal acetate proportion.
Essential oils	Westerhold et al. (2013)	Next enhance (NE) - 300 (contains cinnamaldehyde, garlic, and mineral oil) fed at 0, 150, 300, and 600 mg/steer/d for entire finishing period.	No effect on growth and carcass traits, except for decreased back fat thickness.
Essential oils (microencapsulated)	Alemu et al. (2019)	Microencapsulated blend of essential oils (carvacrol, cinnemaldehyde, and capsaicin) fed at 150 mg/kg DM for a period of 112 days.	No effect on DMI, FE, and ADG.
Essential oils (microencapsulated)	Soltan et al. (2018)	Microencapsulated blend of essential oils at 200 or 400 mg/kg DMI.	Increased nitrogen retention and microbial protein synthesis. No effect on nutrient digestibility and ammonia nitrogen concentration.
Essential oils (microencapsulated)	Spanghero et al. (2007)	REPAXOL feed (contains 0.8% essential oil) added at 10 g/Kg diet and fed for a period of 32 days.	Improved FE and Lower fecal microbial count.

(*continued on next page*)

Table 1 (*continued*)

Class	Reference	Type of PSM, dosage and period fed	Findings of the Research work
Essential oils and non-protein amino acids	Hassan and Abdel-Raheem (2013)	Caraway at 2 g/kg diet or garlic at 2 g/kg diet or their combination for 6 months.	Combination increased ADG and FE.
Essential oils, non-protein amino acid, and other PSMs.	Hill (2007)	Apex dry 3030 mixture (contains garlic, anise, cassia, rosemary, and thyme) fed at 0.5 g/Kg milk replacer or calf starter or both for 56 days.	Faster BWG, Improved FE, and lessened fecal score.
Essential oils and phenol	Seifzadeh et al. (2016)	Medical plant mix (contains 9% thyme, 25% mint, 12% oregano, 25% cumin, 10% camel thorn, 7% garlic, and 12 % Eucalyptus) fed at 1.5 or 3.0 g/calf/d with or without probiotic for 1 month.	Feeding at 1.5 g/calf/d improved feed intake and reduced the weaning age of calf.
Essential oils and phenol	Seifzadeh et al. (2017)	Medical plant mix (contains 9% thyme, 25% mint, 12% oregano, 25% cumin, 10% camel thorn, 7% garlic, and 12% Eucalyptus) fed at Medicinal plant at 1.5 or 3.0 g/calf/d with or without probiotic for one month.	Feeding at 1.5 g/calf/d improved feed intake and reduced the weaning age of calf. Essential oils at higher dosages (3%) decreased the intake, despite combined with probiotics.
Essential oils mixture	Niwas et al. (2013)	Herbstone (Pudina, ajwain, harada, ammi, amla, zinger, chirayita, kalmegh) fed at 20 g/Kg concentrate ration for 60 days.	Increased intake, digestibility coefficients, BWG, length, and girth circumference.
Essential oil mixture in combination with saponins or tannins	Samal et al. (2015)	Mixture – 1: Made up of ajwain oil and lemon grass (contains mixture of essential oils) in 1:1 ratio fed at 0.05% DMI. Mixture – 2: Made up of garlic and soapnut (contain essential oils, non-protein amino acids, and saponins) in 2:1 ratio and fed at 2% DMI. Mixture – 3: Made up of garlic, soapnut, harad, and ajwain (contains essential oils, tannin, and saponin) in 2:1:1:1 ratio and fed at 1% DMI. Three mixtures fed for 8 months.	No effect on nutrient digestibility. Improved FE. Inhibited methane emission.
Fennel powder	Saeedi et al. (2017)	Fennel powder (contains Essential oils (8%), anethole (60–80 %), fenchone (10–30 %), flavonoids, coumarin, and sterols) supplemented at 4 g or 8 g/Kg diet. Fed from birth to 2 weeks post weaning.	Increased pH, molar proportion of propionate, short-chain fatty acids, and growth performance.
Carotenoids	Becker (2013)	Spirulina fed at 2, 6, or 25 g/day for 57 days.	Unaffected BW and FE. Decreased plasma cholesterol concentration.
Sesquiterpenes and HT	Patel et al. (2017)	*Emblica officinalis* and *Tinospora cordifolia* (2:1) fed at 450 mg/kg BW for 28 days.	Decreased serum cortisol and Increased immunogenic effect.
Tannins	Krueger et al. (2010)	HT and CT fed at 14.9 mg/kg DMI for 42 days.	No effect on animal performance and rumen fermentation patterns.
Tannins	Liepa et al. (2018)	*Hippophae rhamnoides* leaf meal extract fed at 5 to 8 ml/calf/twice a day for a period of 1 year.	Increased growth rate. Decreased incidence of diarrhea. Reduced serum haptaglobulin concentration and lymphocytes' count in blood.
Tannins	Min et al. (2006)	Quebracho CT fed at 1 or 2 g CT/kg DMI for a period of 63 days (after 8 weeks adaptation period).	Reduced ruminal microbial activity, biofilm, and ruminal gas production. Increased ADG.
Tannins	Rivera-Mendez et al. (2017)	Trial I – CT at 0%, 0.2%, 0.4%, and 0.6% of DM for 84 days. Trial II – 0% tannin, 0.6% CT, 0.6% HT, 0.3% CT + 0.3% HT for 84 days.	Trial I - Increased BWG and FE. Trial II – Tended to increase ADG and DMI.
Tannins, flavonoids, alkaloids and organic acids.	Varma et al. (2018)	Pomogranate peel extract fed at 4% of the ration for 60 days.	Short-chain VFAs flux was 5.2 times higher in treatment group compared to control.
Triterpenes	Draisci et al. (2007)	Plant sterols at 79 mg/100 g or 87.4 mg/100 g for a period of 65 days.	Increased urinary contents of 17-α boldenone component.
Triterpenoid saponins	Bhati et al. (2017)	*Aloe vera* extract fed at 30 g/Kg diet for 30 days.	Decreased protozoal count and ruminal ammonia - N. Increased nutrient digestibility and growth performance.
Triterpenoid saponins	Nichols et al. (2011)	*Yucca schidigera* extract fed at 1.0 g/steer/day for a period of 189 days.	No effect on BWG and FE. Decreased marbling.
Triterpenoid saponins	Mirza et al. (2002)	*Yucca schidigera* extract fed at 0.5 g/kg urea molasses mineral block for a period of 70 days.	Improved BWG, FE, and economics of feeding.
Triterpenoid Saponin	Yadav et al. (2017)	*Aloe vera* extract fed at 2 or 4 g/kg BW /day for a period of 10 weeks.	Improved BWG and other morphometric parameters.

ADG, average daily gain; BW, Body weight; BWG, Body weight gain; CT, condensed tannins; DMI, dry matter intake; FE, feed efficiency; HT, hydrolysable tannins; NE, next enhance; PSM, plant secondary metabolites; VFA, volatile fatty acids.

boldenone. White scilla (contain steroidal glycosides) has been known to use traditionally for deworming and meconium expulsion in newborn calves (Miller, 1997). Most of the vegetable oils are the richest sources of naturally occurring phytosterols. In a study, Yoho et al. (2012) replaced lard with coconut oil (rich in Δ7-stigmasterol, Δ7-avenasterol, and other phytosterols) at 0%, 20% (56 g/kg diet), and 40% (112 g/kg diet) levels in jersey calves fed with liquid diets. The lard replacements did not affect DMI and average daily gain (ADG), although they managed to improve health status by reducing fecal score.

Saponins constitute a triterpenoid or steroidal aglycone. Saponins primarily inhibit the protozoal population (defaunation), which appears to increase microbial protein synthesis and post-ruminal protein flow. They may also alter the rumen metabolism in a beneficial way by increasing the cell membrane's permeability of few specific rumen bacteria (Arabski et al., 2012). Aloe vera, an herbal source of saponin, was proved to be an effective herbal feed additive for calves due to the ability to decrease ruminal ammonia N (NH_3-N) production and increase nutrient digestibility and growth performance (Bhati et al., 2017). The most convincing evidence for the usage of Aloe vera extract as a feed additive in calves can be obtained from the outcomes of Yadav et al. (2017). They revealed that the supplementation of extract at 2 or 4 g/kg BW/day improved the growth production efficiency and morphometric parameters of calves. *Yucca schidigera,* a desert plant and major marketable source of saponins, could be used as coccidiostat and immune-stimulant (Sahoo et al., 2015). The powder of stem of *Yucca schidigera* was known to improve FE and BWG of zebu calves (Mirza et al., 2002). Several studies on *Quillaja saponaria* (rich in triterpenoid saponins) revealed the presence of important biological properties such as antibacterial, antiviral, antifungal, antiparasitic, and antitumor activities (Fleck et al., 2019). The beneficial effects of Quillaja are well reported in poultry and pigs; yet, the efficacy of their usage has to be explored in calves. Fenugreek saponins are known to exhibit hypocholesterolemic properties (Wani and Kumar, 2018), which promotes their usage in calves to raise designer (low-cholesterol) beef.

3.1.3. Tetraterpenes and polyterpenes

Carotenoids, the accessory pigments of photosynthesis, represent the most significant components of tetraterpenes, and their usage as feed additive primarily owes to the antioxidant potency rather than antibacterial activity. The pre-ruminant calf is considered as an exceptional model to evaluate the absorption and transportation rate of carotenoids, especially for carotenoids that are banned or unaccepted for human feeding studies (Bierer et al., 1995). A Japanese study revealed a higher rate of absorption and accumulation of astaxanthin, echinenone, and β-carotene in calves fed *Xanthophyllomyces dendrorhrous* yeast (rich in xanthophylls) (Tani et al., 2014). Foliage is richer in tetraterpene carotenoids. Hence, the positive results of growth trials involving any leaf extracts might also be attributed to the presence of tetraterpenes. Another important application in calves is the reversal of drug resistance, which can be achieved by administering the drug in association with carotenoids (Wink, 2007). Lycopene is also a phytochemical containing symmetrical tetraterpene units. Asparagus (contains lycopene) was proved to improve growth performance, thereby facilitating the early sexual maturation in Sahiwal calves (Jamra et al., 2016). A feeding trial conducted by replacing rice straw with tomato pomace (contains lycopene) at three replacement levels (35%, 50%, and 65% levels) revealed 35% (350 g/kg diet) as an optimum replacement in economic perspectives, since increasing pomace levels did not affect ADG and FE of growing cattle (Caluya, 1997). This study also reveals that tomato waste from canning industries can be successfully fed to calves without any negative effects on growth performance.

3.2. Phenolics

Phenols or phenolics are a class of chemical compounds consisting of a hydroxyl group (−OH) bonded directly to an aromatic hydrocarbon group. The research conducted by using the phenolic compounds in calves and their results is presented in Table 2.

3.2.1. Phenylpropanoids, coumarins, and furanocoumarins

Major aromatic and lipophilic phenylpropanoids include eugenol, safrol, apiole, myristicin, elemicin, β-asarone, and estragole, which are mainly found in essential oils of Rosaceae, Myristiaceae, and Apiaceae families (Wink, 2015). Phenylpropanoids possess antimicrobial properties either by reacting with thiol (-SH) groups of proteins or by alkylating proteins with DNA (Wink, 2015). Essential oils are also known to possess a defaunating effect, due to the lipophilic nature, which helps these compounds in crossing the protozoal membranes (Zotti et al., 2017; Hassan et al., 2020).

Among the research works collected on the calf-herbal database, nearly 30% of the studies used phenol-based essential oils either directly or in its raw source as a feed supplement to calves. The efficacy of essential oils (oregano extract at 10 mg/kg BW/day) in decreasing mortality rates, severity of scours, and colibacillosis was similar to that of neomycin at an equal proportion (Bampidis et al., 2006). Later, Meyer et al. (2009) also confirmed that essential oils blend could be used as potential alternatives for neomycin in calves. Incorporation of essential oils as a part of the regular calf diet aids in better resistance during unintended stressful situations like dehorning and castration (Mario-Benedetti, 2017). Jeshari et al. (2016) further proved this resistance notion by detecting an improvement in certain immune-physiological parameters on supplementing essential oils to calves exposed to abrupt weaning stress. In another study, supplementation of essential oil mixture (eucalyptus oil, menthol crystal, and mint oil) to either milk or drinking water also instigated better health conditions and post-weaning growth performance (Soltan, 2009). These authors attributed the beneficial growth response to enhanced nutrient digestibility and serum metabolites. Essential oils, at a concentration above 35 mg/l rumen fluid, inhibited certain hyper-ammonia-producing bacteria (McIntosh et al., 2003). Besides essential oils, the residue left after its distillation also possesses antimicrobial activity; therefore, it could positively influence the FE and BWG of calves (Jeshari et al., 2016).

Howbeit, it is not always sure that supplementation of essential oils will inevitably benefit the health and performance of calves.

Table 2
Plant extracts, active components, effect, and calves research of phenolic compounds.

Class	Reference	Type of PSM, dosage and period fed	Findings of the Research work
Anthocyanins and phenolic acids	Palazzo et al. (2017)	Grape pomace fed at 1 kg/head/day for 75 days.	Improved total microbial operational taxonomic units.
Catechins	Sarker et al. (2010)	Neomycin or fermented green tea product fed at 5 g/Kg diet for 150 days.	Similar performance, hematological, and immunological parameters to that of neomycin fed at 110 ppm.
Phenols and essential oils	Mousavi et al. (2014)	A tablet containing *Echinacea purpurae* (500 mg) and *Pelargonium Graveolens* (135 mg) supplemented for 25 days.	Improved γ-Interferon, lactoferrin, and total IgG levels. Half tablet for 5 days was stated as optimum.
Phenols and tannins	Perme (2014)	Harad (*Terminalia chebula*) and garlic at 2% BW or their combination with *Saccharomyces cerevisiae* for 180 days.	No effect on FI, nutrient digestibility, microbial protein, and immune status. Improved FE.
Polyphenol > 30%	Ishihara et al. (2001)	Green tea extract (Teapecus B; Taiyo Kagaku Co. Ltd, Japan) at 1.5 g/day/calf for 30 days.	Improved Bifidobacterium and Lactobacillus species. Decreased *Clostridium perfringens* species.
Flavonoids	Balcells et al. (2012)	Bioflavex [contains naringine (200 g/kg) and grape fruit extract (400 g/kg)] fed for a period of 22 days	Unaffected ADG and FE; Increased propionate production; Decreased incidence of acidosis.
Flavonoids	Bi et al. (2017)	Mulberry flavonoids 5.0% (w/w) fed at 3 gm per calf for 36 days (from 28 to 64 days of age).	Increased ADG, FE, and gut beneficial bacterial count. Decreased fecal score and E.coli K99 count.
Flavonoids	Sarker et al. (2010)	Propolis powder fed at 0.5 g/Kg concentrate mixture for 2 months.	Higher FI and ADG.
Flavonoids	Seradj et al. (2014)	A mixture of citrus flavonoids (contains neoeriocitrine, naringine, isonaringine, hesperidine, neohesperidine, poncirine) incubated at 200 μg/g DM in rumen liquor from growing steers.	Decreased population of hydrogenotrophic methanogenic archaea. Increased propionate production.
Flavonoids	Yang et al. (2010)	Cinnamaldehyde fed at 0, 400, 800, or 1600 mg/finishing calf/day during finishing period.	No effect on growth and carcass traits, except for intake, which increased on supplementation.
Flavonoids, vitamins, and enzymes	Zhang et al. (2017)	Mulberry flavonoids at 2 or 4 g/d along with yeast (*Candida tropicalis*) at 1 g/day for 60 days.	Caused a positive synergistic effect on nutrient digestibility, FI, and growth.
Functional oils	Purevjav (2013)	Essential™ Oligo Basics; USA, LLC mixture (contains Phenylpropanoids (Cashewnut shell oil), Polyterpenes (Castor oil) at 250 mg/kg DMI or 500 mg/kg DMI for 169 days.	Inclusion of function oil at 500 mg/kg DMI increased dressing percentage and carcass characters.
Functional oils	Zotti et al. (2017)	OligoBasics mixture (contains Phenyl-propanoids (cashewnut shell oil), Polyterpenes (castor oil)) fed at 400 mg/kg DMI for 21 days.	No effect on TVFA fraction and feed behavior parameters.
Lignans (phytoestrogens)	Aharoni et al. (2004)	Crushed flax seed at 80 g/kg DM for 300 days.	Increased intramuscular fat and conjugated linoleic acid and other Omega-3 fatty acids in lipid fractions.
Phytoestrogens, iridoid glucosides, and flavonoids	Rani et al. (2006)	*Eclipta alba* (bhringraj) or *Kutaki picorrhiza* (kutki) fed at 0.4% level or their combination (1:1) for 30 days.	Did not have any persistent beneficial effects on the performance up to 77 days growth trial.
Phenols and essential oils	Mousavi et al. (2014)	A tablet containing *Echinacea purpurae* (500 mg) and *Pelargonium Graveolens* (135 mg) supplemented for 25 days.	Improved γ-Interferon, lactoferrin, and total IgG levels. Half tablet for 5 days was stated as optimum.
Phenols and tannins	Perme (2014)	Harad (*Terminalia chebula*) and garlic at 2% BW or their combination with *Saccharomyces cerevisiae* for 180 days.	No effect on FI, nutrient digestibility, microbial protein, and immune status. Improved FE.
Polyphenol > 30%	Ishihara et al. (2001)	Green tea extract (Teapecus B; Taiyo Kagaku Co. Ltd, Japan) at 1.5 g/day/calf for 30 days.	Improved Bifidobacterium and Lactobacillus species. Decreased *Clostridium perfringens* species.

ADG, average daily gain; BW, Body weight; FE, feed efficiency; FI, feed intake; TVFA, volatile fatty acids.

In a study, NEXT ENHANCE (Novus International Ltd.), a commercial essential oil product, was extensively tested for its impact by conducting three *in vivo* trials in finishing calf-fed steers and found variable impacts on animal performance (Bittner, 2016). More recently, Alemu et al. (2019) reported no advantage in crossbred steers supplemented with a microencapsulated blend of essential oils. These results in calves were in corroboration to those reported earlier by Westerhold (2013). On evaluating thyme and cinnamon essential oils in calves, Vakili et al. (2013) also expressed that the usage of essential oils do not influence the growth performance or production parameters, except for altered molar proportions of volatile fatty acids; nevertheless, these results cannot be completely relied upon, as the additives were used for only a shorter period (45 days). Meanwhile, a Brazilian study revealed that supplementing an essential oil blend at different doses (200 or 400 mg/kg) did not influence the performance, fecal score, rumen fermentation, and intestinal fauna of Holstein calves receiving milk replacer at 6 l/day and calf starter *ad libitum* amount (Santos et al., 2015). A recently published dissertation also indicated no significant changes in performance of pre-weaned calves supplemented with a blend of essential oil (thymol, guaiacol, eugenol, vanillin, salicylaldehyde, and limonene) at 300 mg/kg diet, though the incidence of diarrhea and fecal score were reduced (Mario-Benedetti, 2017).

Several inconsistencies appear to be associated with the dosage and chemical structure of the plant metabolite, microbial population, diet composition, extent of adaptation of the microbes to antimicrobial compounds, and age of the calf. For instance, a study compared three sources of essential oils, namely thyme, celery, and eucalyptus with monensin in calf starter diets and revealed that eucalyptus oil was superior in improving the ADG and FE in post-weaning calves compared to the other sources (Akbarian-Tefaghi et al., 2018). The age and weaning status of the calf is another important consideration to be taken into account, as the beneficial effect of essential oils are more prominent in postweaning period compared to pre-weaning calves, because of the underdevelopment of rumen lacking active rumen microbes (Chapman et al., 2017; Seifzadeh et al., 2017). The extent of antimicrobial activity of essential oil compounds primarily depends upon pH of the medium, type of essential oil components, and their inclusion levels. The effect of active components of certain essential oils might be enhanced in low pH due to the conformational changes in their structure, which further increases the sensitivity of bacteria to the structurally altered molecules (Calsamiglia et al., 2007).

Few herbs like fennel powder (Phenylpropanoids) contain appetite stimulants such as anethole and fenchone, which make the calves' starter diets more palatable by increasing the taste (Saeedi et al., 2017). An additive-based study on the cattle finishing programme revealed that inclusion of functional oil mix containing cashew nut shell oil (contains anacardic acid) and castor oil (contains ricinoleic acid) at 250 or 500 mg/kg DMI to calves' diets generates more profitable feeding regimen because of the obtainment of prime grade carcasses and better dressing percentage (Purevjav et al., 2013). But, supplementation of the same functional oil mix at 400 mg/kg DMI did not influence the feed behavior patterns and rumen fermentation variables in abruptly weaned Nellore calves (Zotti et al., 2017). Apart from being the main ingredients of beverages and cosmetic products, coumarins are extensively used for phytoremediation in calves suffering from ailments. Coumarins are well known for their use in alleviating the negative effects of aflatoxins (Hassan et al., 2019). Further, the furanocoumarin compounds, major PSMs in grapefruit and citrus peels, are well known for their antimicrobial potentiality (Politowicz et al., 2017). Although the isolated furanocoumarin components are not directly tested as feed additives, their sources (citrus peels and grapefruit extracts) are certified as safe growth promoters in calves (Rafiq et al., 2016; EFSA, 2016).

3.2.2. Lignans and lignins

Few lignin compounds inhibit the microtubule formation, a basic step in mitotic spindle construction, thereby instigating a bacteriostatic effect. Lignin is known to control intestinal pathogens and increase the BWG in early growing calves. Lignin, especially sulfur-free lignin fractions, such as Alcell, could be used as prebiotic feed additives in calves (Calvo-Flores et al., 2015). Despite the immense acceptance of these products in livestock-based feed industry, limited information exists on feeding lignan-phytoestrogen substances to calves; however, studies in other species affirm many favorable results on their usage. Flaxseed, the most abundant source of phytoestrogens (Lignans), is usually incorporated as feed ingredient rather feed-additive. Including the flax seed ingredients in beef calf rations guarantee higher content of omega-3 fatty acids, which is profitable in designer meat production (Aharoni et al., 2004; Mach et al., 2006).

3.2.3. Flavonoids and anthocyanins

Flavonoids exert antimicrobial properties through various mechanisms such as inhibiting the nucleic acid synthesis, suppressing energy metabolism, and inhibiting the function of cytoplasmic membrane (Gadang et al., 2008). Flavonoids can inhibit the electron or carbon flow in the microbial food chain and prevent the accumulation of hydrogen (Chen and Wolin, 1979). Reduced hydrogen increases the propionate proportion to the expense of butyrate and acetate, which is a significant strategy in reducing methanogenesis. The flavonoids supplementation seems to be more beneficial during the stress period (Olagaray and Bradford, 2019).

Balcells et al. (2012) fed eight Holstein Friesian calves with plant flavonoids extract (Bioflavex containing a blend of Naringine (200 g/kg) and grapefruit extract (400 g/kg)) for 22 days. The results revealed increased titers of lactate consuming bacteria (*megasphaera elsdenii*) along with a shift from acetate to propionate production, therefore decreasing the methanogenic potentiality and incidence of rumen acidosis. Another known antimethanogenic mechanism of action of flavonoids is their potential in directly inhibiting the hydrogenotrophic methanogenic archaea in the rumen (Seradj, 2014).

Supplementation of mulberry flavonoids as antibiotic alternatives to pre-weaned calves pre-challenged with *Escherichia coli* K99, led to an improved ADG and FE with a significant lower fecal score, suggesting the defensive effect of flavonoids against the microbes (Bi et al., 2017). In the same study, the community diversity index of flavonoid fed group showed an increased count of beneficial bacteria like *Prevotella*, *Lactobacillus*, and *Enterococcus*, which are further expected to promote gut health. A recent study also showed that supplementation of flavonoid-rich *Hippophae rhamnoides* leaf meal extract at 5–8 ml/calf twice daily has reduced the serum haptoglobin concentration and incidence of diarrhea, consequently promoting the growth rate (Liepa et al., 2018). Although no improvement was found in growth and carcass traits, supplementation of cinnamaldehyde, a flavonoid of cinnamon, managed to improve intake, due to its appetite-stimulating property (Yang et al., 2010). Further, replacing soybean meal with primerose oil cake (contains flavonoids and tannins), up to 50% (33 g/kg diet), proved to improve FE in calves (Strzetelski et al., 1998). Nevertheless, oral administration of quercetin aglycone, at 50 mg/kg BW, to neonatal calves for a week was neither able to compensate for insufficient colostrum supply nor showed any positive effect on antioxidant or anti-inflammatory status (Gruse et al., 2016). The differences in beneficial effects of flavonoids may be due to the variabilities in dose, specific compound efficacy, and mode of action (Olagaray and Bradford, 2019).

Anthocyanin, a vacuolar pigment related to heart disease, is also known to possess a notable antimicrobial action against microbes, especially gram-positive bacteria, apparently due to its activity on biological membrane and intracellular interactions. Despite the evidence on the beneficial effects of anthocyanins (Changxing et al., 2018), the European food safety authority reported that their usage as feed additives is worth reevaluating due to the inadequate toxicological database (EFSA, 2013). Feeding grape-pomace (anthocyanins, tannins, and phenolic acids) to Holstein Friesian calves at 1 kg/calf daily for a period of 75 days increased the rumen microbial population of *Prevotella stercorea*, *Bacteroides uniformis*, and *Ruminococcus flavefaciens*, albeit no influence was noticed on the overall composition of the rumen microbiota (Palazzo et al., 2017).

3.2.4. Catechins and tannins

Catechins are a distinctive class of flavonoids. The hydroxyl groups of catechins often interact with proteins and form ionic, hydrogen or covalent bonds. Although Tannic acid (hydrolyzable tannins (HT)) is recognized as a food flavoring agent by the European Union list of food flavorings, its usage at higher levels has to be checked over and again while feeding to calves. The safer limit of tannic acid as a feed additive is up to 15 mg/kg feed in all animal species (EFSA, 2014). The catechins interact with proteins on the microbial surface and inhibit tissue adhesion and pathogenicity. Catechins are also able to bypass the protein from ruminal degradation, thereby preserving the protein quality in weaned calves fed superior quality proteins.

Catechins can also additionally abridges with gallotannins and increase the total number of hydroxyl groups to form firm tannin-protein complexes, consequently interacting with protein targets in microbes (Wink and van, 2010). Green tea extract (contains catechin) is established as a safe and useful feed additive for calves with respect to its beneficial effect on GIT microflora. The extract proved to increase bifidobacterium and lactobacillus species with a parallel decrease in *Clostridium perfringens* species within GIT (Ishihara et al., 2001). In another study, Sarker et al. (2010) viewed the fermented green tea product as an efficient substitute feed formula for antibiotics because of the superior FE of the beef calves fed former diets.

The mechanism of antimicrobial action of ellagitannins is diverse and includes adhesion formation, enzyme inhibition, cell wall-complexes formation, substrate deprivation, membrane disruption, and metal ion complexation (Cowan et al., 1999). Because of the bacteriostatic activity of tannins, they are used as exclusive agents to control foodborne pathogens in calves (Min et al., 2008). Supplementation of Quebracho condensed tannin (CT) at 1 or 2% of the BW increased BWG and decreased the bloat scores, biofilm production, and rumen gas production, principally by minimizing the rumen microbial activities (Min et al., 2006). Supplementing different levels of HT or CT to calves resulted in improved BWG and DMI, irrespective of the source and levels of dietary tannins (Rivera-Méndez et al., 2017). However, Krueger et al. (2010) reported no effect of either HT (mimosa extract) or CT (Chestnut extract) supplementation on BWG, FE, and growth performance of calves fed high-grain diet. The study also revealed that there is no apparent cause why tannins could not be added in limited amounts to alleviate pathogens if antimicrobial efficacy is acknowledged.

3.3. Quinones

Hydro-, Naptho-, and Anthra- quinones are the archetypical members of the group. Hydro- and Naptho-quinones are redox reagents and exhibit antimicrobial property by binding to enzymes or interacting with ferrous or ferric proteins such as cytochromes. Most of the anthraquinones possess phenolic OH groups, which accords broad antimicrobial activities by interfering with proteins similar to polyphenols (Kemegne et al., 2017). Withal, the inclusion of anthraquinone substances, at their purest form, is not recommended as long-term feed additives due to their ability to intercalate DNA (Wink and van, 2010).

3.4. Polyacetylenes, polyenes, and alkamides

Polyacetylenes and polyenes possess cytotoxic activity by interfering with membrane proteins and binding to SH groups. Although *Tagetes erecta* (marigold; rich in polyenes and polyacetylenes) extract is primarily known for wound healing in calves (Kumar et al., 2006), its usage as a feed additive is widely accepted in other livestock species, including poultry (Mirzah and Djulardi, 2017). Several polyenes such as amphotericin B, candicidin, trichomycin, nystatin, and pimaricin are used as antifungal agents for therapeutic purposes in calves.

European Union approved Spiramycin, an antimicrobial polyene compound, as a feed additive for calves in 1970, which was later banned in July 1999 because of the resistance notion. Beta carotene, a colored polyene, is considered as a safe feed supplement for all food-producing animals, except veal calves. The EFSA Panel on additives and products or substances used in animal feed (FEEDAP) concluded that *ad libitum* usage of β-carotene as a feed additive in calves should not be encouraged because of the accumulation of pigment in liver that poses a threat to consumer safety (EFSA, 2012). A study conducted on veal calves fed diets with Spirulina (contains provitamin-A carotenoids) at 2, 6, and 25 g/day revealed a significant decrease in the plasma cholesterol concentration without any effect on BW, ADG, and FI (Becker, 2013). The carrot (rich in β-carotene) waste was tested and found to be incorporated up to 400 g/kg diet without any adverse effects on the growth of steers (Rust and Buskirk, 2008). Another study in growing steers found a similar growth performance among the steers fed diets containing ensiled carrots and grass hay compared to those fed on bromegrass and alfalfa silage based ration (Laflamme, 1992).

Alkamides are polyene structures with nitrogen substitutes. They possess potent antimicrobial activity similar to polyenes and add immunostimulant property to few herbs belonging to Echinacea family. Supplementation of Echinacea at 0 or 2.5 g/day for 17 days revealed low serum levels of monocytes and B-cells along with high levels of $CD4^+$ T cells in transitional dairy calves (Gill et al., 2002). Artemisia, another vital source of alkamides, could be used as a potent therapeutic agent against internal parasites in diarrheic calves (Ramadan et al., 2015). The tonic made from the root of *Lepidium meyenii* (rich in alkamides) has been traditionally used to overcome stress and as a fertility enhancer for cattle; yet, its usage as a growth promoter in calves has to be verified with growth trials

(Beharry and Heinrich, 2018).

3.5. Carbohydrates

Few oligosaccharides act as prebiotics, whose beneficial effects have been related to an associated influence of increased Bifidobacteria counts (Liu et al., 2018). They are also known to inhibit the growth and multiplication of potentially pathogenic bacteria such as clostridia, enterobacteria, and salmonella. Mannan oligosaccharides (MOS) positively influence the count of beneficial bacteria and carries the pathogenic microbes out of the host along with the passing digesta. This alteration is achieved by the ability of MOS in anchoring the cell surface-based mannose-binding proteins of few bacterial strains, thus preventing the bacteria from inhabiting the intestinal tract (Ozpinar et al., 2012).

Dietary supplementation of MOS during the pre-weaning period showed encouraging results by beneficially influencing the BWG, FI, FE, and cost per kg gain along with a decreased fecal score and coliform count (Ghosh and Mehla, 2012). Further, their supplementation also managed to reduce the cost of diarrhea treatments and the total number of treatment days, revealing the potentiality of MOS in treatment of diarrhea (Kara et al., 2015). On the contrary, Hill et al. (2008) carried out three trials, in which, the pre-weaned calves were supplemented with different sources of oligosaccharides (Fructo-oligosaccharides and MOS) at altered levels and concluded that supplementation of oligosaccharides did not have any beneficial effects on ADG and FI. The authors reported that neither of the probiotic sources was potential enough against the pathogens causing enteric challenges in the experimental calves. Later, two simultaneous reviews, composed by Roberfroid (2005) and De Vrese and Marteau (2007), appraised the effects of different oligosaccharides on livestock health and performance. They determined that the fructo-oligosaccharides supplementation to pre-weaned calves is beneficial as a prophylactic measure in preventing pathogen-associated diarrhea, but not suitable as a therapeutic agent after attainment of illness. These unpredictable results of MOS on fecal score and growth performance of calves may be related to the different sources of the manufacturer, level and duration of supplementation, diet composition, intestinal bacterial population, health status, and environmental conditions (Kara et al., 2015).

Inulin is a valuable dietary adjunct to manipulate the gut microflora of livestock, especially calves (Samanta et al., 2013). Feeding Jerusalem artichoke flour (contains inulin) at 6, 12, and 24 g/day per calf increased the ADG by the end of the 56th day and improved digestive channel functionality by reducing fecal mass liquefaction (Arne and Ilgaza, 2016). Further, an extensive Polish study revealed that Inulin, at 3 or 6 g/day per calf, was able to improve hemato-biochemical, immunological, and other performance parameters (Krol, 2011). Experimental studies on calves fed a water-soluble polysaccharide isolated from *Physalis alkekengi* var. *francheti* revealed positive effects by increasing the number of lactobacillus species and inhibiting the growth of pathogenic bacteria (Li et al., 2013). These results suggest that use of the extracted polysaccharide may be encouraged as a feed additive in case of GIT microflora imbalances in calves.

3.6. Organic acids

The organic acids, specifically, acetic, malic, fumaric, and citric acid, can penetrate the bacterial cell wall and disrupt the functions of certain pathogenic bacteria (Mishra et al., 2016). They are believed to provide beneficial effects on the host by decreasing the competition among microbes for nutrients. The projection of organic acids as a possible replacement for antibiotics in growing calves is mainly related to the *in vitro* studies' affirmative results in displaying the antimicrobial activity against common pathogenic microbes (Tejero-sarinena et al., 2012). They are more effective against gram-negative bacteria compared to other secondary metabolites, such as essential oils. Organic acids addition to milk may even attenuate certain potential pathogenic microbes such as *Mycoplasma bovis* and *salmonella dublin* (Parker et al., 2016). Another advantage of adding organic acids to milk include the reduced chances of spoilage during preservation, which allows larger quantities of milk at *ad libitum* amounts for calves. Feeding formic acid acidified milk (pH – 4.8) to calves for 6 months decreased the incidence of diarrhea apart from increasing the overall health and well-being (Guler et al., 2006). On the contrary, several works reported no significant changes in the performance of calves supplemented with organic acids through either milk or calf staters (Ribeiro et al., 2009; Hill et al., 2013; Todd, 2013). The inconsistencies in the works mentioned above might be due to altered dosages or forms of organic acids, which play a crucial role in showing significant positive effects. The research and results regarding the usage of quinones, polyacetylenes, carbohydrates, organic acids, and N-containing secondary metabolites in calves are presented in Table 3.

4. Nitrogen-containing secondary metabolites

4.1. Alkaloids

Quite a lot of alkaloids are not often preferred as feed additives in the calf industry because of their intense effect on the host's neuroreceptors through modulation of neuronal signal transduction (Walstab et al., 2014). Few alkaloids such as quaternary benzophenanthridine compounds (Sanguinarine), protopine alkaloids, and isoquinoline alkaloids have been known to use as feed additives in various livestock species, but their effects are yet to be researched in calves (Tschirner et al., 2003; Aguilar-Hernandez et al., 2016). More recently, Varma et al. (2018) supplemented pomegranate peel extract (contains alkaloids in addition to tannins, flavonoids, and organic acids as active components) and found that the extract may promote calves' health and production. However, the authors reported that the peel extract supplementation could alter odor characteristics of feces, thereby increasing the feedlot nuisance and making shed more redolent, if not managed properly.

Table 3
Plant extracts, active components, effect, and calves research of N-containing secondary metabolites, Polyacetylenes, carbohydrates, and organic acids.

Class	Reference	Type of PSM, dosage and period fed	Findings of the Research work
Alkaloids, saponins, and steroidal lactones	Meel et al. (2017)	Aswagandha (*Withania somnifera*) and Reetha (*Sapindus mukorossi*) at 30 g/Kg diet or their combination (1:1) for 30 days.	Increased total protozoal count, concentration of TVFA, NH_3-N, total N, and TCA-precipitable N.
Alkamides	Gill et al. (2002)	Echinacea extract fed at 0 or 2.5 g/day for 17 days.	Decreased monocytes and B-cell percentage. Increased $CD4^+$ T cells.
Inulin	Arne and Ilgaza (2016)	Jerusalem artichoke at 6, 12, and 24 g/calf/day fed for 56 days.	Increased ADG. Improved digestive channel functionality.
Inulin, genosides, and saponins	Devant et al. (2007)	Artichoke (200 – 300 g/kg), ginseng (150 – 250 g/kg) and fenugreek (550 – 650 g/kg) included at 2.8 g/kg DM for 84 days.	No effect on FE and FI. Decreased serum leptin concentration. Increased insulin, cortisol, and propionate.
Non-protein amino acids (alliin, allicin)	Duvvu et al. (2018)	*Allium sativum* fed at 200 or 300 mg/kg BW for 90 days.	Improved FI, FE, ADG, and BCS.
Non-protein amino acids (alliin, allicin)	Ghosh et al. (2011)	Garlic extract fed at 250 mg/kg BW/calf/day for a period of 55 days (from 5 days to 2 months age).	Increased BWG and FI; Decreased severity of scours and E.coli count.
Non protein amino acids and essential oils	Hill et al. (2007)	APEX CMR 3035 (garlic, anise, cassia, rosemary, and thyme) Trial I – Apex at 0.5 g/Kg milk replacer Trial II – Apex at 0.5 g/Kg milk replacer and 0.5 g/Kg calf starter Fed for a period of 56 days.	Increased calf starter intake. Improved BWG.
Oligosaccharides	Ghosh and Mehla (2012)	MOS at 4 g/calf/day for 2 months.	Increased average BWG, intake, and FE. Decreased severity of sours.
Oligosaccharides	Hill et al. (2008)	Trial I – diet supplemented with 4 g Fructo-oligosaccharides /g/ day. Trial II – diet supplemented with 8 g Fructo-oligosaccharides /g/ day. Trial III – diet supplemented with 6 g MOS/g/ day. Trials conducted for 2 months.	No effect on BW, FE, and severity of scours.
Oligosaccharides	Kara et al. (2015)	Celmanex (contains MOS) at 7 g/calf/ day for 56 days.	Reduced days of diarrhea and cost of treatment. Improved fecal score and final BW.
Oligosaccharides and fructose polymer	Krol (2011)	Trial I - MOS fed at 2 or 4 g/calf/ day for 56 days. Trial II – Inulin fed at 3 or 6 g/calf/ day for 56 days.	Improved BWG, FE, volatile fatty acids content and fecal consistency in both the trials.
Organic acid (Formic acid)	Guler et al. (2006)	Formic acid added to milk until pH ranges 4.8. Acidified milk fed at 8% of the BW for 6 months.	Decreased incidence of diarrhea. Improved health status.
Organic acid (Formic acid)	Huuskonen et al. (2011)	1 dL 80% formic acid added to milk and is fed at 6.0 or 10.0 Liter/day for 75 days.	Calves fed higher acidified milk had higher BWG.
Organic acid (microencapsulated)	Spanghero et al. (2007)	ERASE Feed (contains 50% organic acid) fed at 10 g/Kg diet for a period of 32 days.	Improved FE. Lowered fecal microbial activity.
Organic acid mixture	Ribeiro et al. (2009)	Trial I – organic acid mixture (contains citric acid at 400 g, Lactic acid at 180 g, fumaric acid at 20 g, Phosphoric acid at 15 g, and vitamin-C at 5.2 g) at 0.4% of BW in Liquid diet (Milk) for 0–60 days. Trial II – organic acid mixture (contains betaglucans at 80 g, flavonoids at 4 g, linoleic acid at 3 g, oleic acid at 1 g, citric acid at 55 g, and vitamin C at 2.4 g) at 0.5% of BW in solid diet (Concentrate) for 61 to 112 days. Trial III – organic acid mixture (composition similar to trial I) at 0.4% of BW in liquid diet (milk replacer) 0–60 days.	No effect on performance and health status of calves.

ADG, average daily gain; BCS, body condition score; BW, Body weight; BWG, Body weight gain; BWG, Body weight gain; FE, feed efficiency; FI, feed intake; MOS, Mannanoligosaccharides; NH_3-N, ammonia nitrogen; TCA, tri-chloro acetic acid; TVFA, volatile fatty acids.

4.2. Non-protein amino acids

Though the broad antimicrobial properties of alliin and allicin amino acids are well documented, their precise mode of action is unknown. Muller et al. (2016) claim that the antibacterial property of allicin, a non-protein amino acid, might be attributed to the induced thiol stress in bacteria through S-Allylmercapto modification. The beneficial effects of supplementation of onion extract (contains alliin, allicin, and other cysteine derivatives) are well documented in poultry and cattle; yet, the extract has to be experimentally verified in calves (Abad et al., 2017). The antimicrobial efficacy of garlic extract is well testified against certain pathogenic gram-positive (*Staphylococcus saprophyticus*, *Staphylococcus aureus*, *Streptococcus faecalis*, and *Streptococcus pneumonia*) and gram-negative bacteria (*Acinetobacter haemolyticus*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*) (El-Astal, 2004). The results of a trial involving garlic extract supplementation revealed improved performance of the calves in terms of increased mean BWG and FI accompanied by a decreased feed cost/kg gain and severity of scours on a scale of 1–4 (Ghosh et al., 2011). In corroboration to these results, another recent trial also proved that supplementing garlic extract at 200 or 300 mg/kg BW for 90 days improves the production attributes of the buffalo-calves (Duvvu et al., 2018).

4.3. Glucosinolates

Glucosinolates generally exist in the cell vacuoles. The myrosinase enzyme hydrolyzes them into various active forms such as nitriles, thiocyanates, and isothiocyanates on rupture of the cell (Borges et al., 2015). They exert antimicrobial effect by binding to sulfhydryl groups of few pivot enzymes related to bacterial growth and survival (Jacob and Anwar, 2008). Despite the broad antimicrobial activities of glucosinolates, they are not encouraged as feed additives for calves, presumably due to their toxicity. Nevertheless, it was established that glucosinolates, regardless of the source, are not harmful up to 17.50 mmol/g of calves' diet (Tyagi et al., 2008).

4.4. Lectins, peptides and antimicrobial peptides

Lectins possess antimicrobial property due to their ability to inactivate ribosomes, consequently blocking the protein translation. A minor amount of toxic lectins are found in few leguminous species, which may benefit the calf's health on supplementation; however, their safety-threshold is questionable. Plants such as *Ananas comosus* (contains bromelain and ficin) and *Carica papaya* (contains papain) are rich in hydrolytic proteases; and are extensively used as therapeutic agents (Wink, 2015). No calf research was ever conducted on these proteases; nevertheless, results from *in vitro* trials furnish evidence of their antimicrobial property (Anjos et al., 2016), which is assumed to improve the well-being and growth performance of calves.

Antimicrobial peptides of plant origin are often ignored, yet potent in exhibiting the antimicrobial activity towards pathogenic microbes; incredibly, resistant bacterial strains are not exceptional (Aleinein et al., 2014). Supplementing antimicrobial peptides as feed additives provided an immense favorable performance in Juvenile goats. These results could also be applicable to pre-weaned calves due to the similar rumen structure and function between two species.

5. Synergic effects of the plant secondary metabolites

The varied proportion of active components in plants results in synergistic effects on mixing different plant extracts. Hence using a mixture of various plant bioactive components might be beneficial in reducing the required effective dosage. Administration of individual feed additive for an extended period may lead to the development of resistance by the target bacterium. In connection with this, Saeedi et al. (2017) stated that supplementing essential oil compounds alone for an extended period than optimum might cause adaptation of rumen microbes, which further develop resistance to the active ingredients in oils. The synergies among different secondary metabolites of a mixture may often prevent the bacteria from developing resistance by adaptation. This hypothesis explains the reason for successful usage of herbal mixtures since centuries for treating infectious ailments without developing resistance. Besides, an individual component is improbable to comprise all the antibiotics' abilities in creating favorable conditions. Therefore, collective use of diverse herbal or plant extracts as antimicrobial alternatives could provide much more lucrative results. Indeed, it cannot be confirmed that the beneficial effects of most of the aforementioned herb or plant-based studies, presented under different headings, are due to the individual major active component of the plant extract. According to the natural antimicrobial usage database, essential oils and organic acids were the most often mentioned secondary metabolites with additive effects; however, no studies were reported on their synergistic effects in calves (Yang et al., 2015). Theoretically, the essential oils and organic acids work synergistically and produce greater effects. The phenolic compounds of essential oils could damage the integrity of cell membrane, thereby increasing the bacterial vulnerability to acidic environment caused by organic acids. Another notion is that the hydrophobicity of essential oils increases at low pH, allowing it to dissolve at a faster rate in the lipids of the cell membranes of target bacteria (Karatzas et al., 2001).

5.1. Claims of synergistic effects in calf herbal research

A recent investigation on different doses or levels of Echinacea (contains alkamides) and Pelargonium (contains monoterpenoid) revealed an immunomodulatory action by increasing the levels of γ-Interferon, lactoferrin, and total IgG contents. A blend of 250 mg Echinacea and 62.5 mg Pelargonium for a period of 5 days was proposed as an ideal mixture to be supplemented (Seckin et al., 2018). Another blend of plant extracts constituting cynarin, ginseng (contains steroidal glycoside and saponin), and fenugreek (contains saponins and coumarin), at 2.8 g/kg DM diet, was able to display beneficial response on calves' serum and plasma metabolite concentration as equal to those fed diets supplemented with monensin at 32 mg/kg DM (Devant et al., 2007).

Supplementing a combination of harad (contains glycosides and triterpenes) and garlic (contains non-protein amino acids) at 2% of the BW of buffalo calves improved FE, though no improvement was observed in intakes, nutrient digestibilities, population density of ruminal bacteria, immune status, and microbial protein synthesis (Perme, 2014). Another known potential combination is thymol and cinnamaldehyde, which possess the best ability to hinder the multiplication of pathogenic bacteria apart from improving gut vigor (Li et al., 2012). Further, the thymol was also associated with carvacrol and found that the combination was effective enough to increase the ratio of villus height/crypt depth in the distal small intestine and reduce the count of intraepithelial lymphocytes (Michiels et al., 2010). Later, Wall et al. (2014) tried in supplementing the calf starter with a Vegetable (capsicum) – Spice (cinnamaldehyde) – Monoterpenoid phenol derivative (carvacrol) blend and stated that the mixture failed to influence the FE, but managed to increase the average BWG, which has implications in reducing the costs accompanied with animal rearing.

A commercial herbal nutraceutical mixture (Herbastone) was compared to a self-compounded herbal mixture (contains pudina, ajwain, harada, ammi, amla, zinger, chirayita, kalmegh) by incorporating at equal proportions of 2 g/kg concentrate mixture. The authors reported that both the herbal mixtures were able to increase the BWG and other external carcass characteristics by stimulating the appetite and improving the digestibility. They connected the beneficial results to the liver stimulating competence delivered by synergistic herbal coaction (Niwas et al., 2013).

A similar comparison was made among three home-made herbal mixtures namely mix – 1: essential oils blend, mix – 2: saponin and essential oil blend, and mix – 3: tannin, saponin, and essential oil blend and found that all the mixtures were potent enough in decreasing the methane production without any negative effects on the ADG and FE. They also reported that the combination of two essential oil sources gave the best *in vivo* performance compared to the other two blends (Samal et al., 2015). Another commercial herbal product (Apex containing the extracts of anise, thyme, garlic, rosemary, and cassia) was known to improve intake, BW, and FE in Holstein calves fed either all milk crude protein milk replacer or 45% soy protein concentrate milk replacer in a completely randomized design (Hill et al., 2007). The authors attributed these positive results to the blend's antimicrobial potency and improved glucose absorption efficiency. According to an Indian study, a blend of *Tinospora cordifolia* (contains sesquiterpenes) and *Emblica officinalis* (contains HT) is beneficial to calves in inducing non-specific resistance to adverse climatic conditions (causing heat or cold stress) and immunogenic effect with a marked reduction in serum cortisol levels (Patfel et al., 2017). Meanwhile, another study revealed that supplementing Indian ayurvedic herbals like Ashwagandha (contains alkaloids, steroidal lactones, and saponins) and Reetha (contains saponins), either alone or in combination, beneficially altered the rumen fermentation by increasing various nitrogen fractions and short-chain fatty acids in the rumen (Meel et al., 2017). Further, the amalgamation of caraway (contains monoterpenoids) and garlic (contains non-protein amino acids) powders at 2 g/kg diet (DM basis) improved FE and BWG compared to the individual ingredients, presumably due to the synergic effects of alliin and terpenoids (Hassan and Abdel-Raheem, 2013). Recently, Zhang et al. (2017) found a synergic role of mulberry flavonoids and yeast (*Candida tropicalis*) in enhancing the feed intake, growth, and nutrient digestibility.

Feeding a medical plant mix (constitute 9% thyme, 25% mint, 12% oregano, 25% cumin, 10% camel thorn, 7% garlic, and 12% Eucalyptus) for a period of one month before weaning attained threshold feed intake for weaning (1500 g calf starter for 3 consecutive days) faster than control, thus facilitating early weaning in calves (Seifzadeh et al., 2016). In a similarly designed feeding trial, the same authors reported increased daily BWG and decreased fecal, eye, and nasal scores on feeding medicinal plant mix at 1.5 g/calf/day compared to control or 3.0 g/calf/day groups. In another study, Seifzadeh et al. (2017) found no effect while using the combination of essential oils and probiotics for calves. They reported that the higher dosages (3% DMI) of essential oils decreased the dry matter intake, despite combined with probiotics; though the probiotics were hypothesized to have a neutralizing effect on the harmful effects of a higher dosage of essential oils on intestinal microflora. Published outcomes among these synergistic works are variable but showed many encouraging rewards. More research has to be conducted on the appropriate blends, supraphysiological dosages, and routes of herbal additive supplementation to calves.

6. Challenges in supplementing plant secondary metabolites as feed additives for calves

Despite the existence of data on the optimum usage of various natural antimicrobial alternatives on different adult livestock species, their safety and toxicity levels cannot be predicted for young ones until they are completely elucidated and clearly established for calves. Minimal data exist regarding the prescribed amounts or dosage of herbal components to be fed, which is an essential determinant of calf health, welfare, and growth performance. For instance, Ahmed et al. (2009) confirmed that supplementing garlic, lemonade, and anion juices (at a ratio of 1:0.125:1 per liter water) to buffalo calves at 25 g/kg diet improved nutrient utilization, growth rate, and economic efficiency apart from destroying pathogenic microbes. While the same composition mix decreased the ADG on feeding either 50 g/kg or 75 g/kg diet fed, ensuring 25 g/kg as the optimum level among the three inclusion levels. Similarly, the inclusion of oregano extract at 7.5 g/day caused adverse effects on feeding behavior and concentrate intake rather intact or favorable influence (Kolling et al., 2016). Addition of garlic powder at high levels was also known to be associated with a decreased DMI and suppressed DM digestibility (Gholipour et al., 2016). In an Iranian trial, providing fennel powder at 4 g/kg starter diet showed better performance by increasing the propionate proportion and calves' performance compared to that of 8 g/kg diet (Saeedi et al., 2017). Another feeding trial involved in administering essential oils blend at 1.25, 2.5, or 3.75 g/calf/day established the fact that the medium dose (2.5 g) provided optimum results compared to the other two (Froehlich et al., 2017). More recent findings revealed that feeding *Corymbia citriodora* leaf extract at 20 ml/calf/day decreased body weight gains while the same extract at 10 ml/calf/day did not affect the growth performance (Hassan et al., 2020).

Although few metabolites possess a similar mode of action against a common group of pathogenic microbes, the prescribed dose of a single antimicrobial compound does not guarantee alike results of the corresponding metabolite; and is related to the dissimilar minimum inhibitory concentration among various plant-based antimicrobial agents or chemicals (Yang et al., 2015). As a matter of fact, several plant-based (temperature, light, growth, rainfall precipitation, soil, and weather condition) or calf-based (rate of consumption, rate of GIT assimilation, rates of microbial transformation, effect of enzyme inhibition or induction, effect of enzyme inhibition or induction) or diet based (nutrient composition and antinutritional factors percent) factors should be pre-considered while determining the optimum dosage of PSMs. In this regard, a recent work conducted with an aim to evaluate the interactions between the diet composition (18% vs. 20% crude protein content) and essential oils (contains thymol, eugenol, vanillin, limonene, and guaiacol) found an improved BWG, growth, and FE, although no interactions were found between the altered protein contents

(Kazemi-Bonchenari et al., 2018).

It is impracticable to carry out organized and comprehensive assessments towards the safety and efficacy of PSM mixtures because of their multifaceted composition. Besides, the use of PSM-based feed additives is not completely safe and may generate significant interactions with other PSMs or drugs (Elghandour et al., 2018). For instance, the concomitant intake of various CNS-based medicinal drugs and essential oils was known to cause herb-drug interactions (Samojlik et al., 2016). The apigenin and quercetin flavonoids showed antagonistic interaction with few drugs such as flunixin meglumine, erythromycin, and levamisole, which possess prokinetic effects on the GIT (Mendel et al., 2018). Hence, using these flavonoids as feed additives are contraindicated while treating hypomotility disorders in calves. Similarly, β-carotene can interact with proton-pump inhibitors; therefore, they should not be supplemented to calves under the treatment for abomasal ulcers (Kedika et al., 2009). An additive effect was evidenced while subjecting the pathogenic microbes isolated from calf's respiratory tract to doxycycline and thymol essential oils (Kissels et al., 2017). Therefore, the feed provided to the calves on antibiotic therapy should be thoroughly checked for any active PSMs to prevent the additive and toxicity effects. The evidence and mechanism of different herb-drug interactions were well-reviewed by Fasinu et al. (2012).

Very few investigations were made on exploring counteractions among various constituents within a single herb or plant extract, which have to be studied elaborately. Lack of well-developed analytical methods to quantify and identify the traceability of PSMs in calves' tissues is another concern. Further, the PSMs will have multiple actions, including antimicrobial, antioxidant, and immune-modulating effects; therefore, beneficial responses of plant components on calves' performance, if any, could not be attributed to antimicrobial activity alone.

In case of flavor delivering extracts, it is hard to decide whether the improved performance is due to the beneficial effect of herbal extracts or a food flavor effect on starter concentrate. In this regard, Hill et al. (2007) supplemented commercial herbal mixture (apex) to milk or calf starter alone in two different experiments and found increased intake of calf starter in both the trials. The composition of apex (contains anise, thyme, garlic, rosemary, and cassia) is well known to provide flavor effect to the calf starter, thus enhancing the palatability and intake. However, the phenomenon of increased intake of calf starter, even on supplementation of Apex to milk, proves that the beneficial effect of herbal additives on intakes could not be related to flavor alone.

No appropriate information is available on length of the supplementation, which is another indispensable component to be managed while feeding the calves. Feeding for a small number of days could not guarantee the beneficial effect of any active component because of the required adaptation period. An earlier adaptation of the rumen microbes to any PSM to be tested is possible in case of feeding a diet containing similar PSMs before the commencement of *in vivo* study. But, it should also be noticed that majority of the trials do not take history of the feed into account.

The persistence of positive effects is being questioned by commercial farmers from both production and economic points of view. In an innovative study, the persistency of beneficial effects of herbal additives was tested by employing *Eclipta alba* (contains phytoestrogens) or *Kutaki picorrhiza* (contains iridoid glucosides and flavonoids) or a combination of both in 1:1 ratio at 0.44% of the DM intake for a period of 30 days instead of the entire trial period (77 days). Results concluded that the herbal feed additives, either alone or in combination, did not show any persistent beneficial effects on the buffalo calves, except during the period fed (Rani et al., 2006).

It was contended that the feeding trials should be conducted for long periods by using a large number of experimental animals before validating any beneficial effects to recommend for field-level adaptation (Samal et al., 2015). But, the resistance of pathogenic microbes is an unavoidable challenge to be considered while feeding for a longer duration. Recent studies on evaluating the efficacy of few herbal extracts against common clinical isolates revealed microbial resistance to commonly used extracts from plants such as *Syzygium aromaticum* (contains Eugyneol and β-caryophyllene) and *Cinnamomum zeylanicum* (contains Eugenol and Linalool) (Vadhana et al., 2015). Development of resistance can be avoided by using different blends of antimicrobial plant extracts as either feed additives or therapeutics (Ruiz et al., 2017). Further, proper guidance should be required to streamline the data collected for analyzing the extent of antimicrobial resistance in food animals (EFSA, 2019).

Another forsaken focus is the delivery method of phytogenic compounds, which have to be essentially reviewed before supplementing as a feed additive. Microencapsulation of essential oils in a lipid matrix can lower their required effective dosage (Zhang et al., 2005). Few PSMs such as phenylpropanoids possess mutagenic action, and therefore, the dose should be supervised while supplementing at excessive levels within the diet (Wink, 2015). Further, the thermal stability of few compounds, such as essential oils, should be carefully monitored while subjecting the calf starters to any of the processing methods (Olmedo et al., 2014). Furthermore, it is noteworthy that any *in vivo* zoological effect of different plant metabolites is governed by bioavailability, which is a poorly investigated component in calves, unlike poultry and swine.

Comparing diverse studies to arrive at a standard dosage is highly difficult as the results vary with breed, age, feed composition, and environmental conditions. Principally, the efficacies of all PSM's either alone or in combination have been assessed only under experimental environments, which presumably could not reflect the field level animal husbandry conditions. One more ill-explored theme is the safety of public health regarding the accumulation of secondary metabolites in beef or veal from the calves raised on diets containing secondary metabolites. Terpene compounds preferably accumulate in perirenal and peritoneal fat, and the retention of sesquiterpenes in tissues was measured in calves receiving essential oils (Serrano et al., 2007). This finding projects the necessity of considering public health issues while feeding PSMs as feed additives. Furthermore, the profitability of plant extracts is questionable because of the high input costs required for the extract preparation. Often, their usage does not furnish a profitable effect equivalent to that of low-cost synthetic antibiotics.

7. Conclusion

From the antibiotic resistance perspective, administration of plant secondary metabolites to calves provides fascinating results apart from promoting antimicrobial stewardship. Although the published results of various *in vivo* trials in calves were inconsistent, they display many favorable benefits. The individual results presented in the review warrant further confirmation by conducting more *in vivo* studies. Further, the synergistic action of various bioactive components in delivering the health and performance attributes have to be explored thoroughly by examining numerous combinations. These combinations should also need to be tested for drug-herbal interactions before administering as a feed additive to calves, although they are placed under Generally Recognized As Safe category by United States Food and Drug Administration. Moreover, several factors such as starter composition, quantity of milk fed, management system, age of the calf, and status of rumen development have to be considered while evolving the optimum herbal dosage for favorable results. Typically, the frugality data is not available, and hence the feasible and cost-effective herbal formulas should be developed before employing them as feed additives for economically effective and sustainable calf rearing, especially at field level.

Declaration of Competing Interest

None.

References

Abad, P., Arroyo-Manzanares, N., Garcia-Campana, A.M., 2017. Use of onion extract as dairy cows feed supplement: monitoring of PTSO as marker of its effect on milk attributes. J. Agric. Food Chem. 65, 793–799.

Aguilar-Hernandez, M.M., Blunt, M.D., Dobson, R., 2016. IL-4 enhances expression and function of surface IgM in CLL cells. Blood 127, 3015–3025.

Aharoni, Y., Orlov, A., Brosh, A., 2004. Effects of high-forage content and oilseed supplementation of fattening diets on conjugated linoleic acid (CLA) and *trans* fatty acids profiles of beef lipid fractions. Anim. Feed Sci. Technol. 117, 43–60.

Ahmed, A.A., Bassuony, N.I., Awad, E.S., Aiad, A.M., Mohamed, S.A., 2009. Adding natural juice of vegetables and fruitage to ruminant diets (B) nutrients utilization, microbial safety and immunity, effect of diets supplemented with lemon, onion and garlic juice fed to growing buffalo calves. World J. Agric. Sci. 5, 456–465.

Akbarian-Tefaghi, M., Ghasemi, E., Khorvash, M., 2018. Performance, rumen fermentation and blood metabolites of dairy calves fed starter mixtures supplemented with herbal plants, essential oils or monensin. J. Anim. Physiol. Anim. Nutr. 102, 630–638.

Aleinein, R.A., Schäfer, H., Wink, M., 2014. Secretory ranalexin produced in recombinant Pichia pastoris exhibits additive or synergistic bactericidal activity when used in combination with polymyxin B or linezolid against multi-drug resistant bacteria. Biotechnol. J. 9, 110–119.

Alemu, A.W., Romero-Pérez, A., Araujo, R.C., Beauchemin, K.A., 2019. Effect of encapsulated nitrate and microencapsulated blend of essential oils on growth performance and methane emissions from beef steers fed backgrounding diets. Animals 9, 21.

Anjos, D.M., Silva, A.A., Pascoli, I.C., Mikcha, J.M.G., Machinski, J.R., Anjos, D.M.M., Silva, A.A., Pascoli, I.C., Mikcha, J.M.G., Machinski, J.R.M., Peralta, R.M., Filho, A.B.A., 2016. Antibacterial activy of papain and bromelain on Alicyclobacillus spp. Int. J. Food Microbiol. 216, 121–126.

Arabski, M., Gierek-Ciuk, A., Czerwonka, G., Lankoff, A., Kaca, W., 2012. Effects of saponins against clinical E. coli strains and eukaryotic cell line. J. Biomed. Biotechnol. 1, 1–6.

Arne, A., Ilgaza, A., 2016. Different dose inulin feeding effect on calf digestion canal state and development. Livest. Res. Rural Dev. 1, 116–119.

Balcells, J., Aris, A., Serrano, A., Seradj, A.R., Crespo, J., Devant, M., 2012. Effects of an extract of plant flavonoids (Bioflavex) on rumen fermentation and performance in heifers fed high-concentrate diets. J. Anim. Sci. 90, 4975–4984.

Bampidis, V.A., Christodoulou, V., Florou-Paneri, P., Christaki, E., 2006. Effect of dried oregano leaves versus neomycin in treating newborn calves with colibacillosis. J. Vet. Med. A Physiol. Pathol. Clin. Med. 53, 154–156.

Becker, E.W., 2013. Microalgae for human and animal nutrition. Handbook of Microalgal Culture: Applied Phycology and Biotechnology. Chapter 25.

Beharry, S., Heinrich, M., 2018. Is the hype around the reproductive health claims of maca (*Lepidium meyenii Walp*.) justified? J. Ethnopharmacol. 211, 126–170.

Bhati, M., Dhuria, R.K., Sharma, T., Meell, M.S., Saini, S.K., 2017. Effect of *Aloe vera* as herbal feed additive on digestibility of nutrients and rumen fermentation in Rathi calves. Vet. Pract. 18, 282–283.

Bi, Y., Yang, C., Diano, Q., Tu, Y., 2017. Effects of dietary supplementation with two alternatives to antibiotics on intestinal microbiota of preweaned calves challenged with *Escherichia coli* K99. Sci. Rep. 7, 5439.

Bierer, T.L., Merchen, N.R., Erdman, J.W., 1995. Comparative absorption and transport of five common carotenoids in preruminant calves. J. Nutr. 125, 1569–1577.

Bittner, C., 2016. Effects of Feed Additives and Body Weight on Growth Performance and Carcass Characteristics of Beef Finishing Cattle. A dissertation submitted to. University of Nebraska, USA. https://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1140&context=animalscidiss.

Borges, A., Abreu, A.C., Ferreira, C., Saavedra, M.J., Simões, L.C., Simoes, M., 2015. Antibacterial activity and mode of action of selected glucosinolate hydrolysis products against bacterial pathogens. J. Food Sci. Technol. 52, 4737–4748.

Calsamiglia, S., Busquet, M., Cardozo, P.W., Castillejos, L., Ferret, A., 2007. Invited review: essential oils as modifiers of rumen microbial fermentation. J. Dairy Sci. 90, 2580–2595.

Caluya, R., 1997. Tomato Pomace as Cattle Feed. http://agris.fao.org/agris-search/search.do?recordID=PH1998100646.

Calvo-Flores, F.G., Dobado, J.A., Isac-Garcia, J., Marin-Martinez, 2015. Applications of modified and unmodified lignins. Lignin and Lignans as Renewable Raw Materials: Chemistry, Technology and Applications. https://doi.org/10.1002/9781118682784.ch8.

Cannizzo, T.F., Zancanaro, G., Spada, F., Mulasso, C., Biolatti, B., 2007. Pathology of the testicle and sex accessory glands gollowing the administration of boldenone and boldione as growth promoters in veal calves. J. Vet. Med. Sci. 69 (1109-), 1116.

CEC (Commission of the European Communities), Council Directive 2003/74/EC, 2003. Off. J. Eur. Commun. Legis L262, 17.

CEC (Commission of the European Communities), Council Directive 96/22/EC, 1996. Off. J. Eur. Commun. Legis L125, 3.

Changxing, L., Chenling, M., Alagawany, M., Jianhua, L., Dongfang, D., Gaichao, W., Wenyin, Z., Syed, S., Arain, M.A., Saeed, M., Hassan, F.U., Chao, S., 2018. Health benefits and potential applications of anthocyanins in poultry feed industry. Worlds Poult. Sci. J. 74, 251–264.

Chapman, C.E., Hill, T.M., Elder, D.R., Erickson, P.S., 2017. Nitrogen utilization, preweaning nutrient digestibility, and growth effects of Holstein dairy calves fed two amounts of a moderately high protein or conventional milk replacer. J. Dairy Sci. 100, 279–292.

Chen, M., Wolin, M.J., 1979. Effect of monensin and lasalocid-sodium on the growth of methanogenic and rumen saccharolytic bacteria. Appl. Environ. Microb. 38, 72–77.

Cowan, M.M., 1999. Plant products as antimicrobial agents. Clin. Microbiol. Rev. 564–582.

De Vrese, M., Marteau, P.R., 2007. Probiotics and prebiotics: effects on diarrhea. J. Nutr. 137, 803S.

Devant, M., Anglada, A., Bach, A., 2007. Effects of plant extract supplementation on rumen fermentation and metabolism in young Holstein bulls consuming high levels of concentrate. Anim. Feed Sci. Technol. 137, 46–57.

Draisci, R., Merlanti, R., Ferretti, G., Fantozzi, L., Ferranti, C., Capolongo, F., 2007. Excretion profile of boldenone in urine of veal calves fed two different milk replacers. Anal. Chim. Acta 586, 171–176.

Dulebohn, J.H., Bommer, W.H., Liden, R.C., Brouer, R.L., Ferris, G.R., 2011. A meta-analysis of antecedents and consequences of leader–member exchange: integrating the past with an eye toward the future. J. Manag. 38, 1715–1759.

Duvvu, M.V., Rao, K.A., Seshaiah, C.V., Kumar, D.S., 2018. Effect of garlic supplementation on the growth performance and body condition score in Murrah Buffalo

calves. Int. J. Curr. Microbiol. Appl. Sci. 7, 2972–2977.
Ebrahimi, M.A., Sobhanirad, S., Bayat, A.R., 2018. Effects of ajwain (*Trachyspermum ammi*) and thyme (*Thymus vulgaris*) oils on nutrients digestibility, blood parameters and growth performance of brown swiss neonatal calves. Iran. J. Appl. Anim. Sci. 8, 387–395.
EFSA (European Food Safety Authority), Beloeil, P.A., Guerra, B., Stoicescu, A.V., 2019. Manual for Reporting on Antimicrobial Resistance within the Framework of Directive 2003/99/EC and Decision 2013/652/EU for Information Derived from the Year 2018. EFSA Supporting Publication, pp. EN-1559 26 pp.
EFSA (European Food Safety Authority) FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2014. Scientific opinion on the safety and efficacy of tannic acid when used as feed flavouring for all animal species. EFSA J. 12 (3828), 18.
EFSA (European Food Safety Authority) FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2016. Scientific opinion on the safety and efficacy of dry grape extract when used as a feed flavouring for all animal species and categories. EFSA J. 14, 4476.
EFSA (European Food Safety Authority) Panel on Additives and Products or Substances used in Animal Feed (FEEDAP), 2012. Scientific opinion on the safety and efficacy of beta-carotene as a feed additive for all animal species and categories. EFSA J. 10 (2737), 33.
EFSA (European Food Safety Authority) Panel on Food Additives and Nutrient Sources added to Food (ANS), 2013. Scientific opinion on the re-evaluation of anthocyanins (E 163) as a food additive. EFSA J. 11, 340–348.
El-Astal, Z., 2004. The inhibitory action of aqueous garlic extract on the growth of certain pathogenic bacteria. Eur. Food Res. Technol. 218, 460–464.
Elghandour, M.M.M.Y., Reddy, P.R.K., Salem, A.Z.M., Ranga Reddy, P.P., Hyder, I., Barbabosa-Pliego, A., Yasaswini, D., 2018. Plant bioactives and extracts as feed additives in horse nutrition. J. Equine Vet. Sci. 69, 66–77.
European Commission, 2003. Regulation (EC) No. 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. Off. J. Eur. Union L 268, 29–43.
Fasinu, P.S., Bouic, P.J., Rosenkranz, B., 2012. An overview of the evidence and mechanisms of herb-drug interactions. Front. Pharmacol. 3, 1–19.
Fleck, J.D., Betti, A.H., Silva, F.P.D., Trojan, E.A., Olivaro, C., Ferreira, F., Verza, S.G., 2019. Saponins from *Quillaja saponaria* and *Quillaja brasiliensis*: particular chemical characteristics and biological activities. Molecules 24, 171.
Froehlich, K.A., Abdelsalam, K.W., Chase, C., Koppien-Fox, J., Casper, D.P., 2017. Evaluation of essential oils and prebiotics for newborn dairy calves. J. Anim. Sci. 95, 3772–3782.
Gadang, V.P., Hettiarachchy, N.S., Johnson, M.G., Owens, C., 2008. Evaluation of antibacterial activity of whey protein isolate coating incorporated with nisin, grape seed extract, malic acid, and EDTA on a turkey frankfurter system. J. Food Sci. 73, M389–M394.
Gholipour, A., Shahraki, F.A.D., Tabeidian, S.A., Nasrollahi, S.M., Yang, W.Z., 2016. The effects of increasing garlic powder and monensin supplementation on feed intake, nutrient digestibility, growth performance and blood parameters of growing calves. J. Anim. Physiol. Anim. Nutr. 100, 623–628.
Ghosh, S., Mehla, R.K., 2012. Influence of dietary supplementation of prebiotics (mannanoligosaccharide) on the performance of crossbred calves. Trop. Anim. Health Prod. 44, 617–622.
Ghosh, S., Mehla, R.K., Sirohi, S.K., Tomar, S.K., 2011. Performance of crossbred calves with dietary supplementation of garlic extract. J. Anim. Physiol. Anim. Nutr. 95, 449–455.
Gill, N.R., Powel, W., Franklin, S.T., Meek, K.I., 2002. The effects of echinacea on immune function of transitional calves. J. Anim. Sci. 80, 407.
Gruse, J., Kanitz, E., Weitzel, J.M., Tuchscherer, A., Stefaniak, T., Jawor, P., 2016. Quercetin feeding in newborn dairy calves cannot compensate colostrum deprivation: study on metabolic, antioxidative and inflammatory traits. PLoS One 11, e0146932.
Guler, O., Yanar, M., Bayram, B., Metin, J., 2006. Performance and health of dairy calves fed limited amounts of acidified milk replacer. S. Afr. J. Anim. Sci. 36, 149–154.
Hassan, E.H., Abdel-Raheem, S.M., 2013. Response of growing buffalo calves to dietary supplementation of caraway and garlic as natural additives. J. World Appl. Sci. 22, 408–414.
Hassan, A.A., Salma, H., Hafsa, A., Elghandour, M.M.M.Y., Reddy, P.R.K., Monroy, J.C., Salem, A.Z.M., 2019. Dietary supplementation with sodium bentonite and coumarin alleviates the toxicity of aflatoxin B_1 in rabbits. Toxicon 171, 35–42.
Hassan, A., Hafsa, S.H.A., Elghandour, M.M.Y., Reddy, P.R.K., Salem, M.Z.M., Anele, U.Y., Reddy, P.P.R., Salem, A.Z.M., 2020. Influence of Corymbia citriodora leaf extract on growth performance, ruminal fermentation, nutrient digestibility, plasma antioxidant activity and faecal bacteria in young calves. Anim. Feed Sci. Technol. 261, 114394.
Hill, T.M., Aldrich, J.M., Schlotterbeck, R.L., Bateman, H.G., 2007. Apex plant botanicals for neonatal calf milk replacers and starters. Profess. Anim. Sci. 23, 521–526.
Hill, T.M., Bateman, H.G., Aldrich, J.M., Schlotterbeck, R.L., 2008. Oligosaccharides for dairy calves. Profess. Anim. Sci. 24, 460–464.
Hill, T.M., Bateman, H.G., Aldrich, J.M., Quigley, J.D., Schlotterbeck, R.L., 2013. Evaluation of ad libitum acidified milk replacer programs for dairy calves. J. Dairy Sci. 96, 3153–3162.
Ishihara, N., Chu, D.C., Akachi, S., Juneja, L.R., 2001. Improvement of intestinal microflora balance and prevention of digestive and respiratory organ diseases in calves by green tea extracts. Livest. Prod. Sci. 68, 217–229.
Jacob, C., Anwar, A., 2008. The chemistry behind redox regulation with a focus on sulphur redox systems. Physiol. Plant. 133, 469–480.
Jamra, M.S., Mehla, R.K., Sigh, M., Ali, M., Jamra, N., 2016. Effect of *Asparagus racemosus* (Shatavari) feeding on age at sexual maturity in Sahiwal heifers. J. Interacad. 20, 381–386.
Jeshari, M., Riasi, A., Mahdavi, A.H., Khorvash, M., Ahmadi, F., 2016. Effect of essential oils and distillation residues blends on growth performance and blood metabolites of Holstein calves weaned gradually or abruptly. Livest. Sci. 185, 117–122.
Kara, C., Cihan, H., Temizel, M., Catik, S., Meral, Y., Orman, A., Yibar, A., Gencoglu, H., 2015. Effects of supplemental mannanoligosaccharides on growth performance, fecal characteristics and health in dairy calves. Asian-Australas. J. Anim. Sci. 28, 1599–1605.
Karatzas, A., Kets, E., Smid, M.B., 2001. The combined action of carvacrol and high hydrostatic pressure on *Listeria monocytogenes* Scott A. J. Appl. Microbiol. 90, 463–469.
Kazemi-Bonchenari, M., Falahati, R., Poorhamdollah, M., Heidari, S.R., Pezeshki, A., 2018. Essential oils improved weight gain, growth and feed efficiency of young dairy calves fed 18 or 20% crude protein starter diets. J. Anim. Physiol. Anim. Nutr. 102, 652–661.
Kedika, R.R., Souza, R.F., Spechler, S.J., 2009. Potential anti-infl ammatory eff ects of proton pump inhibitors: a review and discussion of the clinical implications. Dig. Dis. Sci. 54, 2312–2317.
Kemegne, G.A., Mkounga, P., Ngang, J.J.E., Kamdem, S.L.S., Nkengfack, A.E., 2017. Antimicrobial structure activity relationship of five anthraquinones of emodine type isolated from Vismia laurentii. BMC Microbiol. 17, 41.
Kertz, F., Hill, T.M., Quingley, J.D., Heinrichs, A.J., Linn, J.G., Drackley, J.K., 2017. A 100-year review: calf nutrition and management. J. Dairy Sci. 100, 10151–10172.
Kissels, W., Wu, X., Santos, R.R., 2017. Interaction of the isomers carvacrol and thymol with the antibiotics doxycycline and tilmicosin: *in vitro* effects against pathogenic bacteria commonly found in the respiratory tract from calves. J. Dairy Sci. 100, 1–5.
Kolling, G.J., Panazzolo, D.M., Gabbi, A.M., Stumpf, M.T., Passos, M.B.D., Cruz, E.A.D., Fischer, V., 2016. Oregano extract added into the diet of dairy heifers changes feeding behavior and concentrate intake. Sci. World J., 8917817 Pp: 1-6.
Krachler, A.M., Orth, K., 2013. Targeting the bacteria-host interface strategies in anti-adhesion therapy. Virulence 4, 284–294.
Krol, B., 2011. Effect of mannanoligosaccharides, inulin and yeast nucleotides added to calf milk replacers on rumen microflora, level of serum immunoglobulin and health condition of calves. Electron. J. Pol. Agric. Univ. 14, 18.
Krueger, W.K., Gutierrez-Bañuelos, H., Carstens, G.E., Min, B.R., Pinchak, W.E., Gomez, R.R., Forbes, T.D.A., 2010. Effects of dietary tannin source on performance, feed efficiency, ruminal fermentation, and carcass and non-carcass traits in steers fed a high-grain diet. Anim. Feed Sci. Technol. 159, 1–9.
Kumar, D., Sharma, S.P., Lugun, A.K., Shekhar, S., Kumar, N., 2006. Efficacy of *Tagetes erecta* as a wound healing agent in buffalo calves. Ind. J. Vet. Surg. 27, 53–54.
Laflamme, L.F., 1992. Carrot/grass silage as cattle feed. Can. J. Anim. Sci. 72, 441–443.
Li, S.Y., Ru, Y.J., Liu, M., Xu, B., Shi, X.G., 2012. The effect of essential oils on performance, immunity and gut microbial population in weaner pigs. Livest. Sci. 145, 119–123.

Li, X., Yang, G., Zhang, C., Wu, D., Tang, L., Xin, Y., 2013. Improvement of intestinal microflora balance by polysaccharide from Physalis alkekengi var. francheti. Mol. Med. Rep. 9, 677–682.
Liepa, L., Zolnere, E., Duritis, I., Krasnova, I., Segliņa, D., 2018. Effects of *Hippophae rhamnoides* L. leaf and Marc extract with reduced tannin concentration on the health and growth parameters of newborn calves. Eur. J. Med. Plants 22, 1–11.
Liu, Y., Espinosa, C.D., Abelilla, J.J., Casas, A., Vanessalagos, L., Woong, A.L., John, B.K., Diego, K.M., Navarro, M.D.L., Jaworski, W., Stein, H.H., 2018. Non-antibiotic feed additives in diets for pigs: a review. Anim. Nutr. 1–13. https://doi.org/10.1016/j.aninu.2018.01.007.
Lorenz, I., Fagan, J., More, S., 2011. Calf health from birth to weaning. II. Management of diarrhoea in preweaned calves. Ir. Vet. J. 64, 9.
Luciano, F.B., Hosseinian, F., Beta, T., Holley, R.A., 2008. Effect of free-SH containing compounds on allyl isothiocyanate antimicrobial activity against *Escherichia coli* O157:H7. J. Food Sci. 73, M214–220.
Mach, N., Devant, M., Diaz, I., Font-Furnols, M., Oliver, M.A., Garcia, J.A., Bach, A., 2006. Increasing the amount of n-3 fatty acid in meat from young Holstein bulls through nutrition. J. Anim. Sci. 84, 3039–3048.
Mario-Benedetti, 2017. Effect of Selected Feed Additives to Improve Growth and Health of Dairy Calves. A Dissertation Presented to the Federal University of Viçosa, as Part of the Requirements of the Graduate Program in Animal Science, to Obtain the Title of Magister Scientiae. http://www.locus.ufv.br/bitstream/handle/123456789/12377/texto%20completo.pdf?sequence=1.
McIntosh, F.M., Williams, P., Losa, R., Wallace, R.J., Beever, D.A., Newbold, C.J., 2003. Effects of essential oils on ruminal microorganisms and their protein metabolism. Appl. Environ. Microbiol. 69, 5011–5014.
Meel, M., Sharma, T., Dhuria, R., Nehra, R., 2017. Rumen fermentation patterns in rathi calves fed complete feed supplemented with herbal feed additives. Int. J. Livst. Res. 7, 63–71.
Mendel, M., Chlopecka, M., Dziekan, N., Karlik, W., 2017. Phytogenic feed additives as potential gut contractility modifiers – a review. Anim. Feed Sci. Technol. 230, 30–46.
Mendel, M., Chlopecka, M., Dziekan, N., Karlik, W., 2018. Interactions between erythromycin, flunixin meglumine, levamisole and plant secondary metabolites towards bovine gastrointestinal motility-*in vitro* study. J. Vet. Pharmacol. Ther. 41, 281–291.
Meyer, N.F., Erickson, G.E., Klopfenstein, T.J., Greenquist, M.A., Luebbe, M.K., Williams, P., Engstrom, M.A., 2009. Effect of essential oils, tylosin and monensin on finishing steer performance, carcass characteristics, liver abscesses, ruminal fermentation, and digestibility. J. Anim. Sci. 87, 2346–2354.
Michiels, J., Missotten, J., Hoorick, A.V., Ovyn, A., Fremaut, D., Smet, S.D., 2010. Effects of dose and formulation of carvacrol and thymol on bacteria and some functional traits of the gut in piglets after weaning. Arch. Anim. Nutr. 64, 136–154.
Miguel, M.G., 2010. Antioxidant and anti-inflammatory activities of essential oils: a short review. Molecules 15, 9252–9287.
Miller, J.S., 1997. Zulu Medicinal Plants: An Inventory By A. Hutchings with A. H. Scott, G. Lewis, and A. B. Cunningham (University of Zululand). University of Natal Press, Pietermaritzburg. 1996. J. Nat. Prod. 60 955-955.
Min, B.R., Pinchak, W.E., Anderson, R.C., Fulford, J.D., Puchala, R., 2006. Effects of condensed tannins supplementation level on weight gain and *in vitro* and *in vivo* bloat precursors in steers grazing winter wheat. J. Anim. Sci. 84, 2546–2554.
Min, B.R., Pinchak, W.E., Merkel, R., Walker, S., Tomita, G., Anderson, R.C., 2008. Comparative antimicrobial activity of tannin extracts from perennial plants on mastitis pathogens. Sci. Res. Essays 3 (2), 66–73.
Mirza, I.H., Khan, A.G., Azim, A., Mirza, M.A., 2002. Effect of supplementing grazing cattle calves with urea-molasses blocks, with and without *Yucaa schidigera* extract, on performance and carcass traits. Asian Australas. J. Anim. Sci. 15, 1300–1306.
Mirzaee, F., Hosseini, A., Jouybari, H.B., Davoodi, A., Azadbakht, M., 2017. Medicinal, biological and phytochemical properties of Gentiana species. J. Tradit. Complement. Med. 7, 400–408.
Mirzah, N., Djulardi, A., 2017. Marigold flower extract as a feed additive in the poultry diet: effects on laying quail performance and egg quality. Int. J. Poult. Sci. 16, 11–15.
Mishra, K., Mishra, V., Qidwai, A., Pandey, A., Shukla, S.K., Pandey, M., Pathak, A., Dikshit, A., 2016. Detoxification and tolerance of heavy metals in plants. Chapter 13. Plant Met. Interact. 335–359.
Mitra, P., Ghosh, T., Mitra, P.K., 2018. Antibiotic resistance and anti-microbial activity of medicinal plants. EC Microbiol. 14, 319–320.
Montoro, C., Ipharraguerre, I., Bach, A., 2011. Effect of flavoring a starter in a same manner as a milk replacer on intake and performance of calves. Anim. Feed Sci. Technol. 164, 130–134.
Mousavi, E.S., Dehghanzadeh, H., Abdali, A., 2014. Chemical composition and essential oils of pelargonium graveolens (Geraniaceae) by gas chromatography–mass spectrometry (GC/MS). Bull. Environ. Pharmacol. Life Sci. 3, 182–184.
Muller, A., Eller, J., Albrecht, F., Prochnow, P., Kuhlmann, K., Bandow, J.E., Leichert, L.I., 2016. Allicin induces thiol stress in bacteria through S-allylmercapto modification of protein cysteines. J. Biol. Chem. 291, 11477–11490.
Nichols, C.A., Jenkins, K.H., Vasconcelos, J.T., Erickson, G.E., Furman, S.A., Goodall, R.S., Klopfenstein, T.J., 2011. Effects of *Lactobacillus acidophilus* and *Yucca schidigera* on Finishing Performance and Carcass Traits of Feedlot Cattle. Nebraska Beef Cattle Report. pp. 72. https://beef.unl.edu/23b2422c-e367-4fe7-b094-b05f5a078e1c.pdf.
Niwas, R., Singh, D.P., Paswan, V.K., Abed, M., Kumar, A.S., 2013. Comparative impact of formulated herbal nutraceuticals on performance of crossbred calves. Bioscan 8, 519–521.
Nsimba, R.Y., Kikuzaki, H., Konishi, Y., 2008. Ecdysteroids act as inhibitors of calf skin collagenase and oxidative stress. J. Biochem. Mol. Toxicol. 22, 240–250.
Obiang-Obounou, B., Kang, O.H., Choi, J.G., Keum, J.H., Kim, S.B., Mun, S.H., Shin, D.W., Woo Kim, K., Park, C.B., Kim, Y.G., Han, S.H., Kwon, D.Y., 2011. The mechanism of action of sanguinarine against methicillin-resistant Staphylococcus aureus. J. Toxic. Sci. 36, 277–283.
Olagaray, K.E., Bradford, B.J., 2019. Plant flavonoids to improve productivity of ruminants—a review. Anim. Feed Sci. Technol. 251, 21–36.
Olmedo, R.V.N., Nepote, V., Grosso, N.R., 2014. Antioxidant activity of fractions from oregano essential oils obtained by molecular distillation. Food Chem. 156, 212–219.
Ozpinar, H., Tekiner, I.H., Gokce, I., 2012. Comparison of LCD-array and real time PCR techniques for detection and verification of animal species in meat products. In: 3rd National Food Safety and Security Congress. 3-4 May, İstanbul, Turkey. pp. 56.
Palazzo, F., Biscarini, F., Castellani, F., Masetti, G., Vitali, A., Grotta, L., Martino, G., 2017. Characterization of the rumen microbiota in dairy calves receiving copper or grape-pomace feed supplementation. Nutrition and feeding – ruminal metabolism. 22nd congress of animal science and production association. Ital. J. Anim. Sci. 16 s1, O010.
Parker, A.M., Shukla, A., House, J.K., 2016. Genetic characterization of Australian Mycoplasma bovis isolates through whole genome sequencing analysis. Vet. Microbiol. 196, 118–125.
Patel, P., Singh, H.S., Mishra, A., Ansari, S.P., 2017. Can *Emblica officinalis* and *Tinospora cordifolia* supplementation possess immunomodulatory and adaptogenic properties in murrah buffalo calves? Indian J. Anim. Res. 51, 506–509.
Perme, B., 2014. Effect of Herbal Feed Additive and *Saccharomyces cerevisiae* on Rumen Methanogenesis and Growth Performance of Male Buffalo Calves. A Dissertation Submitted to Deemed University. Indian Veterinary Research Institute, Izatnagar - 243 122 (U.P.), India.
Politowicz, J., barowska, E.B., Prok, J., Pietr, S.J., Szumny, A., 2017. Antimicrobial activity of essential oil and furanocoumarin fraction of three heracleum species. Acta Pol. Pharm. Drug Res. 74, 723–728.
Purevjav, P.T., Hoffman, M.P., Ishdorj, A., Conover, A.J., Jedlicka, M.E., Prusa, K., Torrent, J., Pusilol, P.A.S., 2013. Effects of functional oils and monensin on cattle finishing programs. The Professional Anim. Sci. 29, 426–434.
Rafiq, S., Kaul, R., Sofi, S.A., Bashir, N., Nazir, F., Nayik, A.G., 2016. Citrus peel as a source of functional ingredient: a review. J Saudi Soc. Agric. Sci. 17, 351–358.
Ramadan, M.Y., Khater, H.F., Abd, E.L., Hay, A.R., Zekry, A.A.M., 2015. Studies on parasites that cause diarrhea in calves. Benha Vet. Med. J. 29, 214–219.
Rani, N., Wadhwa, M., Kaushal, S., Bakshi, M.P.S., 2006. Herbal feed additives and growth of buffalo calves. Anim. Nutr. Feed Technol. 6, 147–151.
Ribeiro, M.D., Pereira, J.C., Queiroz, A.C., Cecon, P.R., Detmann, E., Azevêdo, J.A.G., 2009. Performance of dairy calves fed milk, milk replacer or post-weaning concentrate with acidifiers. Rev. Bras. Zootec. 38, 956–963.

Rivaroli, D.C., do Prado, R.M., Ornaghi, M.G., Mottin, C., Ramos, T.R., Barrado, A.G., Jorge, A.M., do Prado, I.N., 2017. Essential oils in the diet of crossbred (12 Angus vs. 12 Nellore) bulls finished in feedlot on animal performance, feed efficiency and carcass characteristics. J. Agric. Sci. 9, 205–2015.
Rivera-Méndez, C., Plascencia, A., Torrentera, N., Zinn, R.A., 2017. Effect of level and source of supplemental tannin on growth performance of steers during the late finishing phase. J. Appl. Anim. Res. 45, 199–203.
Roberfroid, M.B., 2005. Introducing inulin-type fructans. Br. J. Nutr. 93, S13–S25.
Ruiz, G., Tiffany, T., Erik, N., Linda, S., Jeffrey, L., 2017. Bacterial development of resistance to botanical antimicrobials. J. Evol. Health. 2, 3.
Rust, S., Buskirk, D., 2008. Feeding Carrots or Sugar Beets to Cattle, vol. 13. Michigan State University, Cattle Call, pp. 1–6.
Saeedi, S., Dayani, O., Tahmasbi, R., Khezri, A., 2017. Effect of supplementation of calf starter with fennel powder on performance, weaning age and fermentation characteristics in Holstein dairy calves. J. Anim. Physiol. Anim. Nutr. (Berl). 101, 81–87.
Sahoo, S.P., Kaur, D., Sethi, A.P.S., Sharma, A., Chandra, M., 2015. Evaluation of Yucca schidigera extract as feed additive on performance of broiler chicks in winter season. Vet. World 8, 556–560.
Samal, L., Chaudhary, L.C., Agarwal, N., Kamra, D.N., 2015. Effect of plants containing secondary metabolites as feed additives on rumen fermentation and rumen microbial profile of buffaloes. Anim. Nutr. Feed Tech. 15, 427–437.
Samanta, A.K., Jayapal, N., Senani, S., Kolte, A.P., Sridhar, M., 2013. Prebiotic inulin: useful dietary adjuncts to manipulate the livestock gut microflora. Braz. J. Microbiol. 44, 1–14.
Samojlik, I., Petkovic, S., Stilinovic, N., Vukmirovic, S., Mijatovic, V., Bozin, B., 2016. Pharmacokinetic herb–drug interaction between essential oil of aniseed (*Pimpinella anisum* L., Apiaceae) and acetaminophen and caffeine: a potential risk for clinical practice. Phytother. Res. 30, 253–259.
Santos, F.H.R., Paula, M.D., Lezier, D., Silva, J.T., Santos, G., Bittar, C.M., 2015. Essential oils for dairy calves: effects on performance, scours, rumen fermentation and intestinal fauna. Animal 9, 958–965.
Sarker, M.S.K., Ko, S.Y., Lee, S.M., Kim, G.M., Choi, J.K., Yang, C.J., 2010. Effect of different feed additives on growth performance and blood profiles of Korean Hanwoo calves. Asian-Australas. J. Anim. Sci. 23, 52–60.
Schwarz, S., Loeffler, A., Kadlec, K., 2017. Bacterial resistance to antimicrobial agents and its impact on veterinary and human medecine. Vet. Dermatol. 28, 82–e19.
Seckin, C., Kalayci, G.A., Turan, T., Yilmaz, A., Utku, Y., Aydin, O., Juergen, A., Yilmaz, R.H., 2018. Immunomodulatory effects of Echinacea and Pelargonium on the innate and adoptive immunity in calves. Food Agric. Immun. 29, 744–761.
Seifzadeh, S., Mirzaei, A.F., Abdi-Benemar, H., Seifdavati, J., Navidshad, B., 2016. The effects of a medical plant mixture and a probiotic on performance, antioxidant activity and weaning age of newborn Holstein calves. Iran. J. Appl. Anim. Sci. 6, 285–291.
Seifzadeh, S., Aghjehgheshlagh, F.M., Abdibenemar, H., Seifdavati, J., Navidshad, B., 2017. The effects of a medical plant mix and probiotic on performance and health status of suckling Holstein calves. Italian J. Anim. Sci. 16, 44–51.
Seradj, A.R., 2014. Study the Effect of Inclusion of Feed Flavonoid Substances on Animal Performance and Ruminal Fermentation in Calves. A Dissertation Submitted to Department of Animal Production. University of Lleida, Spain.
Serrano, E., Cornu, A., Kondjoyan, N., Figueredo, G., Agabriel, J., Micol, D., 2007. Terpene accumulation in muscle and fatty tissues of calves supplemented with essential oils. J. Anim. Feed Sci. 16, 168–179.
Soltan, M.A., 2009. Effect of essential oils supplementation on growth performance, nutrient digestibility, health condition of Holstein male calves during pre- and post-weaning periods. Pakistan J. Nutr. 8, 642–652.
Soltan, Y.A., Natel, A.S., Araujo, R.C., Morsy, A.S., Abdalla, A.L., 2018. Progressive adaptation of sheep to a microencapsulated blend of essential oils: ruminal fermentation, methane emission, nutrient digestibility, and microbial protein synthesis. Anim. Feed Sci. Tech. 237, 8–18.
Spanghero, M., Zanfi, C., Fabbro, E., Scicutella, N., Camellini, C., 2007. Effect of milk replacers added with microencapsulated organic acids or essential oils on the performance of weaning calves. Italian J Anim Sci 6 (Suppl. 1) 366-366.
Strzetelski, J.A., Kowalczyk, J., Niwinska, B., Krawezyk, K., Maciaszek, K., 1998. A note on rearing calves on diets supplemented with evening primrose (*Oenothera paradoxa*) oil cake. J. Anim. Feed Sci. 7, 377–383.
Tani, C., Maoka, T., Tani, M., Moritomo, Y., Okada, T., Kitahara, G., 2014. Accumulation of xanthophylls from the Phaffia yeast (*Xanthophyllomyces dendrorhrous*) in calves. J. Oleo Sci. 63, 943–951.
Tejero-Sarinena, S., Barlow, J., Costabile, A., 2012. *In vitro* evaluation of the antimicrobial activity of a range of probiotics against pathogens: evidence for the effects of organic acids. Anaerobe 5, 530–538.
Todd, C.G., 2013. An Investigation Into the Effects of Free-access Acidified Milk Replacer Feeding Programs on the Productivity and Welfare of the Calf. Ph.D. Thesis. The University of Guelph, Canada.
Tschirner, K., Susenbeth, A., Wolffram, S., 2003. Influence of Sangrovit® supplementation on nitrogen balance and feed intake in growing pigs. In: 9th Symposium Vitamins and Additives in the Nutrition of Man and Animal. 2003 Sep. 24–25; Jena: Friedrich Schiller University. pp. 45.
Tyagi, A., Das, S., Singhal, K.K., 2008. Effect of dietary glucosinolates on nutrient utilization and growth of crossbred calves. The Ind. J. Anim. Sci. 78, 510–514.
USDA, 2016. Dairy 2014: Dairy Cattle Management Practices in the United States, 2014. USDA-Animal and Plant Health Inspection Service (APHIS)-Veterinary Services (VS)-Center for Epidemiology and Animal Health (CEAH), Fort Collins, CO. https://www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy14/Dairy14_dr_PartI.pdf.
Vadhana, P., Singh, B.R., Bharadwaj, M., Singh, S.V., 2015. Emergence of herbal antimicrobial drug resistance in clinical bacterial isolates. Pharm. Anal. Acta 6, 10.
Vakili, A.R., Khorrami, B., Danesh- Mesgaran, M., Parand, E., 2013. The effects of thyme and cinnamon essential oils on performance, rumen fermentation and blood metabolites in Holstein calves consuming high concentrate diet. Asian-Aust. J. Anim. Sci. 26, 935–944.
Varma, V.S., Shabtay, A., Yishay, M., Mizrahi, I., Shterzer, N., Freilich, S., Medina, S., Agmon, R., Laor, Y., 2018. Diet supplementation with pomegranate peel extract altered odorants emission from fresh and incubated calves' feces. Front. Sustain. Food Syst. https://doi.org/10.3389/fsufs.2018.00033.
Venkitanarayanan, K., Kollanoor-Johny, A., Darre, M.J., Donoghue, A.M., Donoghue, D.J., 2013. Use of plant-derived antimicrobials for improving the safety of poultry products. Poult. Sci. 92, 493–501.
Vigant, F., Santos, N.C., Lee, B., 2015. Broad-spectrum antivirals against viral fusion. Natural Rev. Microbiol. 13, 426–437.
Wall, E.H., Rodriguez, M., Castillejos, L., Ferret, A., Calsamiglia, S., 2014. The effect of supplementation with a blend of capsicum, carvacrol, and cinnamaldehyde on performance of milk-fed calves. J. Anim. Sci. 92 E-Suppl. 2/J.
Waller, P.J., Bernes, G., Thamsborg, S.M., Sukura, A., Richter, S.H., Ingebrigtsen, K., Hoglund, J., 2001. Plants as de-worming agents of livestock in the Nordic countries: historical perspective, popular beliefs and prospects for the future. Acta Vet. Scand. 42, 31–44.
Walstab, J., Wohlfarth, C., Hovius, R., Schmitteckert, S., Roth, R., Lasitschka, F., Wink, M., Bonisch, H., Niesler, B., 2014. Natural compounds boldine and menthol are antagonists of human 5-HT3 receptors: implications for treating gastrointestinal disorders. Neurogastroenterol. Motil. 26, 810–820.
Wang, L., Fouts, D.E., Stärkel, P., Hartmann, P., Chen, P., Llorente, C., DePew, J., Moncera, K., Ho, S.B., Brenner, D.A., Hooper, L.V., Schnabl, B., 2016. Intestinal REG3 lectins protect against alcoholic steatohepatitis by reducing mucosa-associated microbiota and preventing bacterial translocation. Cell Host Microbe 19, 227–239.
Wani, S.A., Kumar, P., 2018. Fenugreek: a review on its nutraceutical properties and utilization in various food products. J. Saudi Soc. Agri. Sci. 17, 97–106.
Westerhold, M.C., 2013. Essential Oil Effects on Rumen Fermentation, Animal Performance, and Meat Quality of Beef Steers. M.S. Thesis. University of Missouri, Columbia. https://mospace.umsystem.edu/xmlui/bitstream/handle/10355/43035/research.pdf?sequence=1&isAllowed=y.
Wink, M., 2007. Molecular modes of action of cytotoxic alkaloids—From DNA intercalation, spindle poisoning, topoisomerase inhibition to apoptosis and multiple drug resistance. In: In: Cordell, G. (Ed.), The Alkaloids, vol. 64. Elsevier, Amsterdam, The Netherlands, pp. 1–48.
Wink, M., 2015. Modes of action of herbal medicines and plant secondary metabolites. Medicines 2, 251–286.
Wink, M., van, W.Y.K., 2010. Mind-Altering and Poisonous Plants of the World. Timber Press, Portland, OR, USA.
Wolfswinkel, T.L., 2016. The Effects of Feeding Prebiotics, Antibiotics, and Alternative Proteins During the Preweaning Period to Dairy Calves on Growth, Health, and the Gastrointestinal Microbiota. Graduate Theses and Dissertations. https://lib.dr.iastate.edu/etd/15464.
Xie, Y., Yang, W., Tang, F., Chen, X., Ren, L., 2015. Antibacterial activities of flavonoids: structure–activity relationship and mechanism. Curr. Med. Chem. 22, 132–149.

Yadav, A.K., Kumar, S., Barman, R.S.D., Varma, R.K., Jha, D.K., 2017. The effect of Aloe vera on growth and body measurement traits in cross bred calf. Res. J. Chem. Envron. Sci. 5, 37–44.
Yang, W.Z., Ametaj, B.N., Benchaar, C., He, M.L., Beauchemin, K.A., 2010. Cinnamaldehyde in feedlot cattle diets: intake, growth performance, carcass characteristics, and blood metabolites. J. Anim. Sci. 88, 1082–1092.
Yang, C.B., Chowdhury, K.M.A., Hou, Y.Q., 2015. Phytogenic compounds as alternatives to in-feed antibiotics: potentials and challenges in application. Pathogens 4, 137–156.
Yoho, W.S.B., Swank, V.A., Eastridge, M.L., O'Diam, K.M., Daniels, K.M., 2012. Jersey calf performance in response to high-protein, high-fat liquid feeds with varied fatty acid profiles: intake and performance. J. Dairy Sci. 96, 2494–2506.
Zhang, K.Y., Yan, F., Keen, C.A., Waldroup, P.W., 2005. Evaluation of microencapsulated essential oils and organic acids in diets for broiler chickens. Int. J. Poult. Sci. 4, 612–619.
Zhang, L.Y., Qu, P.B., Tu, Y., Yang, C.T., Diao, Q.Y., 2017. Effects of flavonoids from mulberry leaves and candida tropicalis on performance and nutrient digestibility in calves. Kafkas Univ. Vet. Fak. Derg. 23, 473–479.
Zhang, X., Chen, D., Xu, G., Huang, W., Wang, X., 2018. Molecular epidemiology and drug resistant mechanism in carbapenem-resistant Klebsiella pneumoniae isolated from pediatric patients in Shanghai, China. PLoS One 13, e0194000. https://doi.org/10.1371/journal.pone.0194000.
Zotti, C.A., Silva, A.P., Carvalho, R., Marino, C.T., Rodrigues, P.H.M., Silva, L.F.P., 2017. Monensin and a blend of castor oil and cashew nut shell liquid used in a high-concentrate diet abruptly fed to Nellore cattle. J. Anim. Sci. 95, 4124–4138.