



Review article

Coping with shrub secondary metabolites by ruminants

R.E. Estell*

USDA-ARS, Jornada Experimental Range, Box 30003, MSC 3JER, Knox Street, Las Cruces, NM 88003, USA

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ABSTRACT

Rangelands throughout the world contain varying but often substantial proportions of shrubs. Shrubs are generally heavily chemically defended, and herbivores must either contend with their plant secondary metabolites (PSM) or avoid a significant component of the available forage. Browsing ruminants are exposed to thousands of chemicals in infinite combinations and concentrations that are constantly changing both temporally and spatially. The success with which a herbivore navigates this complex environment is in part attributed to its ability to cope with PSM. Plant secondary metabolites can affect a number of physiological and metabolic processes (e.g., altered microbial activity, reduced digestion, compromised acid/base balance, toxicity), although negative consequences to the herbivore range from harmless to lethal, depending factors such as dose, animal species, plane of nutrition, and physiological state. Herbivores have a variety of intertwined mechanisms to cope with consumption of PSM, ranging from physiological (e.g., salivary proteins, detoxification pathways) to behavioral (e.g., avoidance, regulation of intake below critical threshold, cautious sampling, altering size and pattern of feeding bouts, diet switching, consuming diverse and/or complementary diets). Secondary compounds may affect requirements for nutrients (e.g., protein, minerals, and glucose) and water, and may alter basal metabolic rate. Energy requirements may also increase to accommodate increased travel to water and supplementation sites to counter these negative effects, particularly on arid rangelands. A number of management strategies exist for minimizing the negative effects of PSM consumption on livestock. Supplementation to replace nutrients depleted during detoxification (e.g., amino acids and glucose), additives such as PEG and charcoal to reduce absorption and increase excretion of PSM, maintaining animals in good body condition, and behavioral modifications (e.g., diet training) are among the potential management options for enhancing the ability of ruminants to cope with PSM when browsing shrubby ecosystems.

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1. Introduction

About 25% of the world's land surface is used for extensive livestock production, and over a fourth of this grazed land is dominated by shrubs (Asner et al., 2004). Shrubs are generally well defended and have survived and often flourished under systems receiving heavy grazing. These shrubs are typically used by browsing ruminants in low

amounts if at all, even though they often contain an abundance of protein and other nutrients. Secondary chemistry of shrubs across arid and semi-arid regions represents a basic mechanism for plant competitiveness and appears to be especially important for adaptation to harsh, resource-limited environments (Freeland, 1991). Thousands of PSM from numerous structural classes exist in nature, and their presence and concentration in a given plant are influenced by genetics, phenology, and a host of biotic and abiotic environmental factors. Thus, their concentrations vary temporally and spatially among and within species, and their proportions relative to other compounds (both

* Corresponding author. Tel.: +1 575 646 4842; fax: +1 575 646 5889.
E-mail address: restell@nmsu.edu.

primary and secondary) are in constant flux. While there is little doubt that secondary chemistry plays a pivotal role in herbivory, the mechanisms by which ruminants cope with PSM and effect of secondary compounds on livestock production are not well understood.

2. Consequences of PSM consumption

The variable nature of secondary chemistry of plants is the basis for differential use within and among plant species. In one of the first studies to demonstrate differential use of a shrub species by ruminants, Welch et al. (1981) reported varying preference for certain accessions of sagebrush (*Artemisia tridentata*) by mule deer (*Odocoileus hemionus*). Studies conducted at the Jornada Experimental Range (JER) revealed differential use of tarbush (*Flourensia cernua*) by small ruminants. Variable plant to plant defoliation by sheep and goats was related to concentrations of epicuticular wax and specific mono- and sesquiterpenes on the leaf surface (Estell et al., 1994, 1998a). Preference and/or intake of browse species have been negatively related to terpene concentration (either total amount, specific fractions, or individual compounds) in mule deer (Personius et al., 1987; Schwartz et al., 1980b), red deer (*Cervus elaphus*) (Duncan et al., 1994), roe deer (*Capreolus capreolus*) (Vourc'h et al., 2002), sheep (Estell et al., 1998b, 2002; Ngugi et al., 1995), and goats (Riddle et al., 1996). Preference and/or intake of woody browse species have also been negatively related to phenolic and/or tannin concentrations (total phenolics, hydrolyzable tannins, condensed tannins, or individual compounds) in African antelope (*Aepyceros melampus* and *Tragelaphus strepsiceros*) (Owen-Smith and Cooper, 1985), fallow deer (*Dama dama*) (Alm et al., 2002), moose (*Alces alces*) (Stolter et al., 2005), and sheep and/or goats (Degen et al., 2002; Papachristou et al., 2003; Provenza and Malechek, 1984; Silanikove et al., 1996; Woodward and Coppock, 1995). Salem et al. (2006) reported that condensed tannins, total phenolics, saponins, alkaloids, and essential oil were all good predictors of intake by sheep and goats consuming Egyptian browse species.

In addition to effects on intake and dietary preferences, secondary compounds exert other effects ranging from decreasing diet quality to microbial effects to toxicosis. Shrubs containing terpenes, tannins, or phenolics can adversely affect dry matter and/or protein digestibility and nitrogen retention (Hagerman et al., 1992; Kaitho et al., 1998a; Min et al., 1998; Ngugi et al., 1995). Tannins can also shift site of protein digestion (increase ruminal escape protein) and nitrogen excretion (from urine to feces) in ruminants (Kaitho et al., 1998b; Woodward and Reed, 1997), due to their ability to bind and precipitate protein (Mueller-Harvey, 2006). Silanikove et al. (1996) observed reduced serum urea concentration in goats fed shrubs containing tannins, which they attributed to low nitrogen availability. Tannins also bind carbohydrates to some extent (Mueller-Harvey, 2006), which may also have implications for fermentation and nutritional value of some diets.

Secondary compounds also exert indirect effects on microbes that ultimately impact animal status. Phyto-

chemicals that negatively affect rumen bacteria can alter not only extent of digestion, but also fermentation patterns and end products available for metabolism. For example, phenolic acids (including *p*-coumaric acid) can be toxic to ruminal cellulolytic bacteria (Hartley and Akin, 1989), while saponins have been reported to increase microbial nitrogen flow from the rumen and decrease methane production, presumably due to defaunation of ruminal protozoa (Abreu et al., 2004; Babayemi et al., 2004). Terpenes can decrease *in vitro* digestibility in ruminants due to negative microbial effects (Oh et al., 1967; Schwartz et al., 1980a). Broudiscou et al. (2007) reported that with the exception of α -pinene, individual terpenes generally reduced fermentation *in vitro*. However, Malecky et al. (2009) observed no effect of a blend of four monoterpenes on digestion or fermentation in goats and low recovery from the duodenum; they suggested the difference compared to their previous *in vitro* study was due to the long (several weeks) adaptation period. While the mechanisms by which PSM influence digestion and metabolism vary among compounds and classes, some generalizations exist. For example, condensed tannins tend to be poorly absorbed and not particularly toxic, but negatively influence digestion and protein status; conversely, hydrolyzable tannins are more readily absorbed and exert toxic effects at the tissue level.

Once absorbed, mammals rely on a combination of biotransformation enzyme systems (particularly in the liver, kidney, and intestines) for detoxification (e.g., oxidation, reduction, hydrolysis, and conjugation) (Parkinson and Ogilvie, 2008). Although in some cases biotransformation can increase toxicity (Parkinson and Ogilvie, 2008), phase I reactions increase polarity (and water solubility) and typically decrease toxicity of nonpolar lipophilic compounds through addition of functional groups via mixed function oxidases of cytochrome P450 enzymes (e.g., oxidation, hydrolysis, reduction), resulting in production of organic acids for urinary excretion (Dearing et al., 2005; Foley et al., 1999). The resulting decrease in blood pH must be countered by bicarbonate and phosphate buffering systems and elimination of hydrogen ions in the form of ammonium chloride (primarily via ammonia from hepatic glutamine) (Guyton, 1991). Phase II reactions involve detoxification through conjugation of PSM with compounds such as amino acids (e.g., glycine), glucuronic acid, glutathione, and sulfates, producing conjugates for excretion in bile or urine (e.g., glucuronides, hippuric acid); this process is energetically more expensive because of the loss of attached molecules, but avoids the physiological demands of excretion of acidic end products (Dearing et al., 2005; Foley et al., 1999).

The consequences of PSM ingestion at the tissue level are variable and dose dependent, and the degree and site of damage depend on many factors. The physiological implications of ingestion of secondary compounds range from nearly harmless (or even positive) to lethal, depending on the how acutely toxic a compound is and/or whether the quantity ingested is sufficient to overwhelm detoxification systems. For example, saponins are surfactants that can cause cellular membrane damage and red blood cell hemolysis but tend to be poorly absorbed (Majak, 2001; Marston

and Hostettmann, 1991). Alkaloids can interfere with cellular processes such as DNA, RNA, protein replication, transcription, synthesis, and membrane integrity (Wink, 1998). Many PSM cause organ and tissue damage (i.e., gastroenteritis, intestinal necrosis, nephritis, hepatotoxicity); furthermore, intestinal lesions can alter permeability and increase absorption of compounds that are not normally absorbed (e.g., condensed tannins) (Murdiati et al., 1992; Reed, 1995).

3. Coping mechanisms

Ruminants cope with PSM through integrated behavioral and physiological mechanisms that involve both pre-ingestive (sensory) and post-ingestive processes. Behavioral strategies to cope with PSM include reduced consumption, avoidance (especially bitter compounds), cautious sampling to attain familiarity with consequences, selecting plants/parts with lower concentrations, temporary intake cessation, changing pattern of feeding, altering diet composition, increasing dietary breadth/diet mixing, regulating PSM intake below a critical threshold, consuming dietary constituents to counter PSM, and consuming soil (Boyle et al., 2005; Dziba et al., 2006; Freeland and Janzen, 1974; Marsh et al., 2006a; Wiggins et al., 2003; Wink, 1998).

Odor, texture, and taste are integrated to create specific flavors and flavor intensities to which an animal perceives and responds, and through which an animal can associate a particular food with its post-ingestive consequences and modify feeding behavior accordingly (Burritt and Provenza, 2000; Launchbaugh et al., 1993). Previous experience (early life as well as long-term), novelty/familiarity and flavor generalization, learning (from dam and peers), and metabolic state all affect the ability of an animal to create and maintain aversions and preferences (Burritt and Provenza, 1989; Distel and Provenza, 1991; Frost et al., 2003; Villalba and Provenza, 2000). Learning occurs on a continual basis through processes such as sampling, trial and error, and social interactions (Provenza et al., 1992). Learning can occur through associational cues that alert an animal to an aversive compound that is imperceptible prior to its action on the emetic system (Lawler et al., 1999; Moore et al., 2004). However, complex environments may increase the number of pre-ingestive cues required to assess the value of a given food and decrease learning efficiency (Favreau et al., 2010; Ginane et al., 2005). For example, Duncan and Young (2002) observed goats fed one of three conifer species individually in conjunction with positive, neutral, or negative post-ingestive stimuli selected for and against the appropriate species in subsequent preference tests. Yet, when all three species were fed together and goats were dosed with a mixture of the same stimuli, goats tended to select a mixed diet and had greater difficulty associating the feedback with a particular diet component. Thus, learning to equate feedbacks with the appropriate food may be hampered by simultaneous availability of multiple plants such as would be encountered by free-ranging animals (Duncan and Young, 2002).

Cautious sampling and diet mixing may also allow detoxification enzymes to be maintained at an induced

state as a protective mechanism in the event of PSM consumption (McLean and Duncan, 2006). Elevated blood PSM concentrations can cause feeding to decrease or cease, causing some herbivores to modify feeding patterns spatially and/or temporally to regulate PSM intake and blood metabolites below a critical threshold (Boyle et al., 2005; Dziba et al., 2006; McLean and Duncan, 2006; Pfister et al., 1997). Dziba et al. (2006) observed both ruminal and intravenous infusion of 1,8-cineole decreased intake by lambs, and suggested the combined effects of absorption, distribution, and excretion operate together to halt feeding and determine length of cessation. Dziba and Provenza (2008) fed lambs diets containing monoterpenes in concentrations representing multiples found in sagebrush and observed they regulated dry matter intake such that terpene intake plateaued at approximately 28 g/d.

Consuming diverse and/or complementary diets is a behavioral strategy to cope with PSM and allows increased shrub consumption. Varied chemical exposure within and among plant species can benefit herbivores in terms of increasing intake of shrubs containing PSM. The general strategy for diet selection in a variable chemical environment is for the herbivore to optimize nutrient intake and minimize toxin intake (Belovsky and Schmitz, 1994; Freeland and Janzen, 1974). The detoxification limitation theory assumes animals can consume more toxin-containing forages of greater chemical diversity because detoxification is spread over more metabolic pathways, thereby reducing constraints on enzymes and substrates (Marsh et al., 2006a). Complementary feeds contain PSM that exert negative effects through different routes. Complementary feeds may contain secondary compounds with different sites of toxicity (e.g., a poorly absorbed PSM that causes intestinal damage and a readily absorbed compound detoxified in the liver) or compounds that are absorbed and detoxified by different enzyme systems. An animal should theoretically be able to consume more total food when two complementary foods are available compared to a single food (or two non-complementary feeds). However, pathways are not completely independent because detoxification is complex in terms of toxin detection, requirements for enzymes, co-substrates, ATP supply, acid/base balance regulation, end product removal, etc. (Marsh et al., 2006b).

Complementarity has been suggested to be the basis for modified intake and/or feeding behavior reported for a variety of species and conditions (Burritt and Provenza, 2000; Freeland et al., 1985; Wiggins et al., 2003). Villalba et al. (2004) found sheep fed diets containing oxalates, tannins, or terpenes consumed more total feed when offered in pairs than when fed individually, and when all three were fed at one time, sheep consumed as much total feed as controls receiving no PSM. Papachristou et al. (2007) reported that when amount of high quality food was restricted during conditioning, sheep learned to mix with feeds containing PSM (oxalates, tannins, or terpenes), and this diet mixing continued later when nutritious alternatives were available *ad libitum*. Increasing dietary botanical diversity by feeding more high-tannin Mediterranean shrub species to sheep and goats generally increased total shrub intake (Rogosic et al., 2006a, 2006c, 2007), and providing

a shrub containing saponins along with the same high-tannin shrubs increased intake even more in both sheep and goats (Rogosic et al., 2006a, 2007). The fact that intake increased with number of species fed even when represented by a single class (tannins) (Rogosic et al., 2006a, 2007) may be because an animal is less likely to consume as much of a specific toxin, since classes of PSM are not mutually exclusive (i.e., a high-tannin shrub likely contains a variety of other PSM) and even within a class, chemical structures and properties are variable (Rogosic et al., 2008). Every shrub species (even within species) likely has unique chemical (both primary and secondary) profiles that contribute to unique flavors and nutritional values; thus, it is not unexpected that diet diversity would improve intake (Rogosic et al., 2008).

Herbivores can modify behaviors both temporally and spatially to minimize PSM intake and/or allow time for detoxification/elimination in order to maintain blood levels at metabolically acceptable levels. Specific behaviors that animals employ to regulate PSM intake in time and/or space include adjusting level of intake, rate of intake, length and/or number of feeding bouts, intake per feeding bout, total feeding time, length between feeding bouts, diet switching, and changing locations (tree to tree, shrub to shrub, patch to patch, etc.) (Marsh et al., 2006b, 2007; Wiggins et al., 2003, 2006a), and the response among individual animals is quite variable (Marsh et al., 2007). Diet switching is similar to complementarity but does not necessarily involve different classes of PSM (the switch may simply be from high to less/none of the compound causing a transient aversion). Pattern of intake may be as important for coping with PSM as total amount consumed (Foley et al., 1999). Much excellent work regarding intake behavior and meal pattern alterations in response to PSM has been conducted with marsupials, but research on ruminants is sparse. Perevolotsky et al. (2006) reported that tannins can alter feeding behavior of small ruminants by causing more and shorter feeding bouts. Dziba and Provenza (2008) reported lambs fed diets containing monoterpenes in concentrations representing multiples of those in sagebrush decreased intake as terpene concentration increased, but also exhibited a temporal pattern of feed intake, in that lambs receiving diets with higher terpene concentrations spent more time eating later in the feeding period, thereby spreading intake over a longer timeframe. Much more work needs to be done to determine the role played by secondary compounds in behavior of ruminants on extensive landscapes.

In addition to altered behavior, herbivores are equipped with various anatomical (e.g., species with prehensile lips are more adept at selecting specific plant parts) and physiological (body size, production of salivary proteins, site of fermentation, passage rate, etc.) attributes that influence how animals cope with PSM consumption. Some browsers secrete proline-rich salivary proteins that complex with tannins and negate their detrimental effects; while browsers (e.g., deer) synthesize these proteins, grazers such as cattle and sheep do not (Makkar and Becker, 1998; Mueller-Harvey, 2006; Robbins et al., 1987). These complexes are generally stable and excreted in the feces (Shimada, 2006). Goats typically consume more browse

than sheep or cattle and appear to be better able to cope with PSM than other domestic ruminants (Rogosic et al., 2006b; Salem et al., 2006; Utsumi et al., 2009). Lamy et al. (2009) did not detect proline-rich proteins in parotid saliva from goats or sheep receiving a tannin-free diet; however, Alonso-Díaz et al. (2010) did find evidence of tannin-binding proteins in saliva of goats consuming tropical tannin-rich plants. Some mammalian species have other mechanisms to cope with PSM, such as the presence of efflux transporters (e.g., permeability glycoproteins) in gut enterocytes of specialist woodrats that secrete compounds back into the intestinal lumen to minimize absorption (Sorensen and Dearing, 2006) and excretion of highly oxidized metabolites by marsupials in lieu of more energetically expensive conjugation pathways (Boyle et al., 1999). Whether adaptations such as these occur in ruminants is unknown.

Ruminants have certain unique abilities to cope with PSM related specifically to rumen function. Plant volatiles such as terpenes may be partially eliminated during mastication and eructation before negative consequences occur (Cluff et al., 1982). Furthermore, rumen microbes can adapt to PSM (Duncan et al., 2000; Oh et al., 1967). For example, Duncan et al. (2000) showed adapting goats to oxalic acid increased its ruminal degradation and altered subsequent diet selection by increasing proportional intake of plants with high oxalic acid content. Because of rumen microbial activity, ruminants are often exposed to a different array of secondary compounds than originally consumed. Broudisou et al. (2007) showed that extent of ruminal degradation of individual mono- and sesquiterpenes was highly variable. Thus, for this class of compounds, the profile consumed vs. that present for absorption may be quite different. In certain situations, microbes protect ruminants from toxins because they are degraded and rendered less toxic via pre-gastric fermentation (Duncan et al., 2000; Freeland and Janzen, 1974). Conversely, microbial PSM metabolism can actually increase toxicity. For example, hydrolysis of cyanoglucosides and glucosinolates to sugars and aglycones releases cyanide and thiocyanates, respectively (Kakes, 1991; Majak, 2001), and pyrogallol (a hepatotoxic and nephrotoxin) is formed by rumen microbes from gallic acid (Murdiati et al., 1992; Reed, 1995).

The ability to cope with PSM is also affected by physiological status and plane of nutrition of the animal. Protein and energy status are both critical for detoxification because processes such as synthesis of detoxification enzymes, supply of carbohydrate and amino acid (AA) precursors for conjugation/excretion, and maintenance of acid/base balance to compensate for acidic end product formation can all deplete nutrients; thus, supplementation may improve nutrient balance and allow animals to consume more PSM (Foley et al., 1999; Illius and Jessop, 1995, 1996). Protein (Villalba et al., 2002a) and energy (Banner et al., 2000) supplementation have been reported to increase intake of sagebrush by sheep and goats. Utsumi et al. (2009) showed that sheep and goats fed protein supplements nearly doubled intake of one-seed juniper (*Juniperus monosperma*) compared to controls. Furthermore, rumen degradable (RDP) and undegradable protein (RUP) supplements differed in their effects during different seasons; for

sheep, RDP generally increased juniper intake compared to RUP or controls, whereas goats had greater juniper intake with RDP supplementation in summer but RUP resulted in greater intake in winter. Although it has been repeatedly stated that the relationship between protein supplementation and PSM consumption relates to increased AA supply to overcome the limits of detoxification, this assertion has not been verified in ruminants.

Protein supplementation also improved intake of diets containing condensed tannins (Villalba et al., 2002b), likely through ameliorating the protein-precipitating properties of condensed tannins. Shaw et al. (2006a) found that sheep fed a high quality diet (both protein and energy) consumed more total toxins from three diets with different toxins vs. sheep fed a low quality diet. Even though ruminants exhibit nitrogen recycling that may assist with maintaining nitrogen balance and coping with PSM-laden shrubs (Nuñez-Hernandez et al., 1989), studies demonstrating a relationship between intake/preference and PSM often involve animals on a low nutritional plane, with less pronounced effects observed on high quality diets (Villalba and Provenza, 2005). Even with a higher nutritional status, animals may not increase PSM intake unless no alternatives exist (Villalba and Provenza, 2005). A threshold likely exists above which supplementation does not exert a positive effect on intake of PSM-laden shrubs. Utsumi et al. (2009) illustrated that protein supplementation increased intake of juniper during spring, summer, and winter seasons, but not during fall. The lack of response during fall coincided with PSM concentrations that were approximately double that during the other three seasons.

In addition to the more widely accepted costs to protein and energy status, PSM may also have implications for mineral and water balance. Altered acid-base balance due to PSM ingestion and acidotic conditions produced during detoxification (Dearing et al., 2005; Foley et al., 1999) can lead to sodium imbalances in some mammalian species (Foley et al., 1999; Iason and Palo, 1991). Iason and Palo (1991) reported that European hares (*Lepus europaeus*) exhibited a severe negative sodium balance when fed phenolics extracted from birch (*Betula pendula*), possibly because cations such as sodium are excreted in conjunction with anions generated during PSM metabolism (Foley et al., 1999). Other minerals (e.g., potassium) may also be compromised in the process of maintaining acid-base balance as herbivores attempt to maintain homeostasis.

Dearing et al. (2001) observed that PSM in one-seed juniper increased water intake and urine output of a generalist woodrat (*Neotoma albigena*) by almost twofold, and decreased urine osmolarity in both specialist (*Neotoma stephensi*) and generalist species. These researchers reported a diuretic effect of PSM in the specialist (2.5-fold more urine per ml of water intake on juniper vs. control), and noted diuresis may be help explain mineral wasting observed previously, because minerals (e.g., sodium) are lost due to lower renal reabsorption as kidneys attempt to cope with high urine output. Dearing et al. (2002) also reported that generalist woodrats (*Neotoma* spp.) exhibited higher water intake and urine output and lower osmolarity when consuming creosote bush (*Larrea tridentata*) resin or α -pinene (i.e., diuretic effects with two classes of com-

pounds: phenolics and monoterpenes), and suggested that because α -pinene is a predominant terpene in one-seed juniper, it may be responsible for the diuretic effects of juniper. However, an alternative mechanism for thirst and increased water intake may be stimulation and irritation of the trigeminal nerve (Dearing et al., 2002).

Research in these areas has been conducted with small wildlife species, and whether PSM affect mineral balance and water loss in ruminants is unknown. However, observations at the JER lend support to the possibility that water balance is at least partially compromised by consumption of shrubs containing secondary compounds. Water consumption was monitored during the last two weeks of a study in which sheep were fed tarbush at 0, 10, 20, or 30% of the diet mixed with a low quality grass for four weeks. Water intake varied among treatments, with the control significantly lower in most cases and numerically lower in every case than for sheep consuming tarbush (King et al., 1996a). Tarbush is high in both phenolics and terpenes (Estell et al., 1996; Tellez et al., 2001), which may stimulate water intake via a diuretic effect or through stimulation of the trigeminal nerve. However, water intake must be interpreted cautiously because of occasional leakage from fistulae in these animals. In a companion study in which sheep were fed the same tarbush/grass diets for three weeks (King et al., 1996b), daily urine output during the last five days did not differ. However, urine volume was highly variable, and daily output was numerically about two- to threefold higher for the 20 and 30% diets vs. the 0 and 10% diets. Water intake was not monitored and intake (therefore terpene intake) was much lower in the second study (approximately 1% of BW vs. nearly 2% in the first study). Although speculative, diuretic effects resulting from ingestion of PSM could have major implications for animals in arid environments (Dearing et al., 2001).

Mangione et al. (2004) observed increased water intake as woodrats (*Neotoma lepida*) increased creosote bush resin consumption, but rather than a diuretic effect, they observed increased fecal water loss. These workers also observed greater energy loss with resin intake, which they attributed to losses associated with glucuronides and/or other conjugation products, since energetic costs associated with detoxification and excretion of PSM (e.g., glucuronic acid) may affect energy requirements (Lamb et al., 2004). Boyle and Dearing (2003) reported that one-seed juniper consumption by woodrats (*Neotoma* spp.) decreased resting metabolism rate, in contrast to their expectations (expected increased metabolism rate to facilitate detoxification). Sorensen et al. (2005) observed decreased energy availability due to PSM consumption, as both urine and fecal energy excretion increased in response to one-seed juniper intake in both specialist (*N. stephensi*) and generalist (*N. albigena*) woodrats. Furthermore, specialists increased intake and decreased basal metabolic rate and locomotor activity, while generalists decreased only activity (Sorensen et al., 2005). Dilution of food energy, negative effects on digestion and absorption of nutrients, and costs of metabolism and excretion are energetic consequences/costs generally associated with PSM intake, and decreased BMR and reduced activity may be strategies to compensate for energy loss (in addition to increased intake

if it can be tolerated, and reduced growth and reproduction) (Sorensen et al., 2005). Besides the well accepted costs of PSM for digestion and detoxification, costs associated with energy and water should be considered (Mangione et al., 2004). The roles of secondary compounds in physiological processes such as nutrient balance, energetics, and water balance could have major implications for livestock and wildlife managers, particularly for large herbivores in arid environments that must travel substantial distances for water.

4. Management considerations

Given the potential for PSM consumption to cause diuresis and affect water balance, mineral loss, energy requirements, metabolism, and activity, it could well be that in addition to energy and protein for detoxification, secondary compounds have major implications for requirements for water and minerals. Maintenance energy requirements may be affected if basal metabolism is altered (depending on direction of change), and travel required to seek water and minerals could increase energy needs. Moreover, if herbivores alter movement on a landscape to optimize PSM intake, this behavior could further increase maintenance requirements as animals attempt to avoid, complement, or switch diets. Although the limited information on this subject has been obtained using small mammals (other than anecdotal evidence of King et al., 1996a, 1996b with tarbush), if these generalizations hold true for ruminants and large wildlife species, PSM could have considerable importance in terms of managerial practices such as water spacing, supplementation, forced movement, etc. Supplementation to meet additional energy requirements, counteract mineral losses, and protein supplementation to enhance enzymatic machinery are managerial decisions that may minimize effects of PSM. Strategic location of supplements and water may allow animals to move among chemical patches more effectively. These issues might be particularly critical on extensive arid landscapes in which both water and high quality forage resources (and even mineral supplements) may be far apart.

Spatial PSM variation must occur on a relevant scale for diet mixing to realistically occur, and could have implications for search costs (Marsh et al., 2006a). Interpatch zones might be preferred locations for diet mixing (Marsh et al., 2006a). If diet switching exists at a scale that has a cost, it may have implications for intake and efficiency; thus, the scale of spatial heterogeneity for a given environment may affect foraging decisions and the ability of a herbivore to optimize diet switching and maximize intake (Wiggins et al., 2006a). When chemically heterogeneous plants are in closer proximity (fine scale heterogeneity) and animals can switch more easily with less traveling, they eat more, eat more often and at a higher rate, and have increased foraging efficiency, which ultimately improves their ability to cope with PSM (Wiggins et al., 2006b). Thus, at a fine scale, animals may simply exhibit differential use to cope with chemical variation, while at a broad scale, animal movement and distribution may be affected by chemical distribution.

A variety of management tools are available to enhance the use of shrubs, thereby tapping a vast nutrient storehouse and extending the forage base. Dziba et al. (2007) reported that sheep provided a choice of high protein and high energy supplements daily for 15 min increased sagebrush intake compared to unsupplemented animals. Manipulating method of introducing a shrub species (e.g., incrementally increasing exposure over time) may provide opportunities to enhance long-term shrub consumption (Animut et al., 2004). Also, body condition may affect propensity of animals to consume PSM, as Frost et al. (2008) reported that goats in low body condition consumed more redberry juniper (*Juniperus pinchotii*) than goats in high body condition. Additives such as PEG, charcoal, and alkaline treatments (e.g., CaOH₂) may prove useful management options for helping ruminants cope with PSM (reduce absorption and/or increase excretion) and enhance use of nonpreferred shrubs (Banner et al., 2000; DeCandia et al., 2000; Landau et al., 2000; Mueller-Harvey, 2006; Provenza et al., 2000; Rogosic et al., 2008; Villalba and Provenza, 2001). Sheep fed free-choice PEG regulated its intake in response to tannin intake (Provenza et al., 2000) and spent more time in locations where PEG was present when consuming high-tannin diets (Villalba and Provenza, 2002). Perevolotsky et al. (2006) noted altered browsing behavior (increased number/decreased length of feeding bouts) of small ruminants consuming high-tannin shrubs was restored when PEG was fed. Glycine is another dietary additive that could potentially enhance detoxification and intake of PSM-containing plants (Marsh et al., 2005); in their study, possums (*Trichosurus vulpecula*) fed diets with benzoate plus glycine exhibited higher intake than when fed either component alone, presumably because benzoic acid is excreted conjugated with glycine (i.e., hippuric acid). Whether supplements containing specific combinations and levels of AA might increase the efficiency with which ruminants cope with PSM is unknown.

Proportions of plants (e.g., high-tannin vs. high-terpene) may affect utilization, and seeding high-tannin shrubs in areas containing high-terpene shrubs may conceivably increase use of terpene-containing shrubs (Mote et al., 2007). Diet training and behavioral modification may also be exploited to cope with and/or increase PSM consumption. Familiarity with a diet that is in adequate supply and high quality may reduce the use of diets containing toxins and prevent animals from learning about complementary interactions with high quality diets containing PSM (Shaw et al., 2006a). Animals experienced with toxins may exhibit greater dietary breadth and eat more plants containing PSM even when nutritious alternatives are available; consequently, training animals to eat various feed combinations (e.g., short term restriction, altered timing of preferred diets) may increase uniformity of use and help prevent shrub encroachment on rangelands (Papachristou et al., 2007; Villalba et al., 2004). Order of encounter of diets differing in PSM concentration (Alm Bergvall and Leimar, 2005) or class of PSM (Mote et al., 2008) can impact intake and preference of ruminants; thus, sequence of exposure may have implications for manipulating shrub use. Utsumi et al. (2010) demonstrated that goats (alone or mixed species with sheep) in

high density treatments spent more time browsing one-seed juniper than those on low density treatments, and all four treatments were associated with increased branch mortality compared to control shrubs. In a study by Shaw et al. (2006b), increased stocking density and exposure time (which reduce alternatives) both increased sagebrush use by sheep. Furthermore, in subsequent preference tests using the same animals under high density stocking, sagebrush use was greatest for animals originally in the high density treatment, intermediate for those on the three-day high density stocking, and lowest for the low density treatment. Thus, restricting alternative diet choices may be a way to teach animals about complementarity and train them to use less desirable plants (Provenza et al., 2007; Shaw et al., 2006b). If herbivores can learn (or be trained) to self medicate and capitalize on complementary PSM, planting forage patches with specific attributes for animals to use as needed (avoiding wholesale group treatment) could be a management option (Villalba and Provenza, 2007).

5. Conclusions

While chemical variability makes it difficult for animals to easily learn the consequences of ingestion, animals have adapted to PSM by learning to avoid certain food sources over time and by developing mechanisms to cope with ingested compounds. Animals generally exhibit low initial preference for PSM-laden shrubs and physiological feedbacks often reinforce aversions over time. Coupled with the fact that PSM can compromise physiological processes and even cause toxicity at certain doses, it is probably unrealistic (and undesirable in certain situations) to expect ruminants to consume shrubs in large quantities or for extended periods. In other cases (e.g., use of supplements/medicines) it may be plausible, but whether these practices are cost effective remains to be seen. Costs of consuming PSM may be especially important in extensive systems if water and energy balance and travel affect metabolic costs. Yet ruminants do utilize shrubs at times to some extent, albeit often in small amounts. Thus, it may be more reasonable to target situational shrub browsing in specific conditions. Use of shrub-friendly species (i.e., goats) is an obvious way to utilize shrub-infested range-lands. Additives may be most beneficial during specific times when fewer alternatives are available or when protein is limiting. Use may be targeted during specific seasons when PSM concentrations are lowest. While diet training in pen studies has been successful in some cases (particularly with few choices and restriction of high quality alternatives), under field conditions it has been limited by the animal's ability to integrate multiple signals from complex environments. Diet training in artificial conditions would require additional expense and labor, and would likely need periodic reinforcement. Management practices such as overnight penning or rapid rotation into smaller homogenous areas could reduce environmental complexity, but would be counter to the concepts of complementarity and biochemical diversity. While it may not be possible at present to significantly increase shrub use in most situations, our challenge remains to seek novel methods to modify browsing ruminants in ways that remove

obstacles to shrub use. Ultimately, our goal is to further expand the forage base and minimize or eliminate livestock grazing impacts on biodiversity.

References

- Abreu, A., Carulla, J.E., Lascano, C.E., Diaz, T.E., Kreuzer, M., Hess, H.D., 2004. Effects of *Sapindus saponaria* fruits on ruminal fermentation and duodenal nitrogen flow of sheep fed a tropical grass diet with and without legume. *J. Anim. Sci.* 82, 1392–1400.
- Alm, U., Birgesson, B., Leimar, O., 2002. The effect of food quality and relative abundance on food choice in fallow deer. *Anim. Behav.* 64, 439–445.
- Alm Bergvall, U., Leimar, O., 2005. Plant secondary compounds and the frequency of food types affect food choice by mammalian herbivores. *Ecology* 86, 2450–2460.
- Alonso-Díaz, M.A., Torres-Acosta, J.F.J., Sandoval-Castro, C.A., Hoste, H., 2010. Tannins in tropical tree fodders fed to small ruminants: a friendly foe? *Small Rumin. Res.* 89, 164–173.
- Animut, G., Goetsch, A.L., Estell, R.E., Merkel, R.C., Dawson, L.J., Sahlu, T., Puchala, R., 2004. Effects of methods of exposure to Eastern red cedar foliage on cedar consumption by Boer crossbred wether goats. *Small Rumin. Res.* 54, 197–212.
- Asner, G.P., Elmore, A.J., Olander, L.P., Martin, R.E., Harris, A.T., 2004. Grazing systems, ecosystem responses, and global change. *Annu. Rev. Environ. Resour.* 29, 261–299.
- Babayemi, O.J., DeMeyer, D., Fievez, V., 2004. *In vitro* rumen fermentation of tropical browse seeds in relation to their content of secondary metabolites. *J. Anim. Feed Sci.* 13 (Suppl. 1), 31–34.
- Banner, R.E., Rogosic, J., Burritt, E.A., Provenza, F.D., 2000. Supplemental barley and charcoal increase intake of sagebrush by lambs. *J. Range Manage.* 53, 415–420.
- Belovsky, G.E., Schmitz, O.J., 1994. Plant defenses and optimal foraging by mammalian herbivores. *J. Mammal.* 75, 816–832.
- Boyle, R., Dearing, M.D., 2003. Ingestion of juniper foliage reduces metabolic rates in woodrat (*Neotoma*) herbivores. *Zoology* 106, 151–158.
- Boyle, R., McLean, S., Brandon, S., Wiggins, N., 2005. Rapid absorption of dietary 1,8-cineole results in critical blood concentration of cineole and immediate cessation of eating in the common brushtail possum (*Trichosurus vulpecula*). *J. Chem. Ecol.* 31, 2775–2790.
- Boyle, R., McLean, S., Foley, W.J., Davies, N.W., 1999. Comparative metabolism of dietary terpene, p-cymene, in generalist and specialist folivorous marsupials. *J. Chem. Ecol.* 25, 2109–2126.
- Broudisou, L.P., Cornu, A., Rouzeau, A., 2007. *In vitro* degradation of 10 mono- and sesquiterpenes of plant origin by caprine rumen microorganisms. *J. Sci. Food Agric.* 87, 1653–1658.
- Burritt, E.A., Provenza, F.D., 1989. Food aversion learning: ability of lambs to distinguish safe from harmful foods. *J. Anim. Sci.* 67, 1732–1739.
- Burritt, E.A., Provenza, F.D., 2000. Role of toxins in intake of varied diets by sheep. *J. Chem. Ecol.* 26, 1991–2005.
- Cluff, L.K., Welch, B.L., Pederson, J.C., Brotherson, J.D., 1982. Concentration of monoterpenoids in rumen ingesta of wild mule deer. *J. Range Manage.* 35, 192–194.
- Dearing, M.D., Foley, W.F., McLean, S., 2005. The influence of plant secondary metabolites on the nutritional ecology of herbivorous terrestrial vertebrates. *Ann. Rev. Ecol. Evol. Syst.* 36, 169–189.
- Dearing, M.D., Mangione, A.M., Karasov, W.H., 2001. Plant secondary compounds as diuretics: an overlooked consequence. *Am. Zool.* 41, 890–901.
- Dearing, M.D., Mangione, A.M., Karasov, W.H., 2002. Ingestion of plant secondary compounds causes diuresis in desert herbivores. *Oecologia* 130, 576–584.
- DeCandia, M., Sitzia, M., Cabiddu, A., Kababya, D., Molle, G., 2000. The use of polyethylene glycol to reduce anti-nutritional effects of tannins in goats fed woody species. *Small Rumin. Res.* 38, 157–164.
- Degen, A.A., Benjamin, R.W., Abdraimov, S.A., Sarbasov, T.I., 2002. Browse selection by Karakul sheep in relation to plant composition and estimated metabolizable energy content. *J. Agric. Sci.* 139, 353–358.
- Distel, R.A., Provenza, F.D., 1991. Experience early in life affects voluntary intake of blackbrush by goats. *J. Chem. Ecol.* 17, 431–450.
- Duncan, A.J., Frutos, P., Young, S.A., 2000. The effect of rumen adaptation to oxalic acid on selection of oxalic-acid-rich plants by goats. *Br. J. Nutr.* 83, 59–65.
- Duncan, A.J., Hartley, S.E., Iason, G.R., 1994. The effect of monoterpene concentrations in Sitka spruce (*Picea sitchensis*) on the browsing behaviour of red deer (*Cervus elaphus*). *Can. J. Zool.* 72, 1715–1720.

- Duncan, A.J., Young, S.A., 2002. Can goats learn about foods through conditioned food aversions and preferences when multiple food options are simultaneously available? *J. Anim. Sci.* 80, 2091–2098.
- Dziba, L.E., Hall, J.O., Provenza, F.D., 2006. Feeding behavior of lambs in relation to kinetics of 1,8-cineole dosed intravenously or into the rumen. *J. Chem. Ecol.* 32, 391–408.
- Dziba, L.E., Provenza, F.D., 2008. Dietary monoterpenes concentrations influence feeding patterns of lambs. *Appl. Anim. Behav. Sci.* 109, 49–57.
- Dziba, L.E., Provenza, F.D., Villalba, J.J., Atwood, S.B., 2007. Supplemental energy and protein increase use of sagebrush by sheep. *Small Rumin. Res.* 69, 203–207.
- Estell, R.E., Fredrickson, E.L., Anderson, D.M., Havstad, K.M., Remmenga, M.D., 1998a. Relationship of tarbush leaf surface terpene profile with livestock herbivory. *J. Chem. Ecol.* 24, 1–12.
- Estell, R.E., Fredrickson, E.L., Anderson, D.M., Havstad, K.M., Remmenga, M.D., 2002. Effects of four mono- and sesquiterpenes on the consumption of alfalfa pellets by sheep. *J. Anim. Sci.* 80, 3301–3306.
- Estell, R.E., Fredrickson, E.L., Anderson, D.M., Mueller, W.F., Remmenga, M.D., 1994. Relationship of tarbush leaf surface secondary chemistry to livestock herbivory. *J. Range Manage.* 47, 424–428.
- Estell, R.E., Fredrickson, E.L., Havstad, K.M., 1996. Chemical composition of *Flourensia cernua* at four growth stages. *Grass Forage Sci.* 51, 434–441.
- Estell, R.E., Fredrickson, E.L., Tellez, M.R., Havstad, K.M., Shupe, W.L., Anderson, D.M., Remmenga, M.D., 1998b. Effect of volatile compounds on consumption of alfalfa pellets by sheep. *J. Anim. Sci.* 76, 228–233.
- Favreau, A., Baumont, R., Duncan, A.J., Ginane, C., 2010. Sheep use preingestive cues as indicators of postingestive consequences to improve food learning. *J. Anim. Sci.* 88, 1535–1544.
- Foley, W.J., Iason, G.R., McArthur, C., 1999. Role of plant secondary metabolites in the nutritional ecology of mammalian herbivores: how far have we come in 25 years? In: Jung, H.J.G., Fahey Jr., G.C. (Eds.), Nutritional Ecology of Herbivores. Proc. 5th Inter. Symp. Nutr. Herbivores. Amer. Soc. Anim. Sci., Savoy, IL, pp. 130–209.
- Freeland, W.J., 1991. Plant secondary metabolites: biochemical coevolution with herbivores. In: Palo, R.T., Robbins, C.T. (Eds.), Plant Defenses Against Mammalian Herbivory. CRC Press, Boca Raton, FL, pp. 61–81.
- Freeland, W.J., Calcott, P.H., Anderson, L.R., 1985. Tannins and saponin interaction in herbivore diets. *Biochem. Syst. Ecol.* 13, 189–193.
- Freeland, W.J., Janzen, D.H., 1974. Strategies in herbivory by mammals: the role of plant secondary compounds. *Am. Nat.* 108, 269–289.
- Frost, R.A., Launchbaugh, K.L., Taylor Jr., C.A., 2008. Age and body condition of goats influence consumption of juniper and monoterpene-treated feed. *Rangel. Ecol. Manage.* 61, 48–54.
- Frost, R.A., Scott, C.B., Walker, J.W., Hartmann, F.S., 2003. Effects of origin, experiences early in life, and genetics on bitterweed consumption by sheep. *Appl. Anim. Behav. Sci.* 84, 251–264.
- Ginane, C., Duncan, A.J., Young, S.A., Elston, D.A., Gordon, I.J., 2005. Herbivore diet selection in response to simulated variation in nutrient rewards and plant secondary compounds. *Anim. Behav.* 69, 541–550.
- Guyton, A.C., 1991. Regulation of acid–base balance. In: Guyton, A.C. (Ed.), Textbook of Medical Physiology, eighth ed. W.B. Saunders, Philadelphia, PA, pp. 330–343.
- Hagerman, A.E., Robbins, C.T., Weerasuriya, Y., Wilson, T.C., McArthur, C., 1992. Tannin chemistry in relation to digestion. *J. Range Manage.* 45, 57–62.
- Hartley, R.D., Akin, D.E., 1989. Effect of forage cell wall phenolic acids and derivatives on rumen microflora. *J. Sci. Food Agric.* 49, 405–411.
- Iason, G.R., Palo, R.T., 1991. Effects of birch phenolics on a grazing and a browsing mammal: a comparison of hares. *J. Chem. Ecol.* 17, 1733–1743.
- Illius, A.W., Jessop, N.S., 1995. Modeling metabolic costs of allelochemical ingestion by foraging herbivores. *J. Chem. Ecol.* 21, 693–719.
- Illius, A.W., Jessop, N.S., 1996. Metabolic constraints on voluntary intake in ruminants. *J. Anim. Sci.* 74, 3052–3062.
- Kaitho, R.J., Umunna, N.N., Nsahlai, I.V., Tamminga, S., Van Bruchem, J., 1998a. Utilization of browse supplements with varying tannin levels by Ethiopian Menz sheep. 1. Intake, digestibility and live weight changes. *Agroforest. Syst.* 39, 145–159.
- Kaitho, R.J., Umunna, N.N., Nsahlai, I.V., Tamminga, S., Van Bruchem, J., 1998b. Utilization of browse supplements with varying tannin levels by Ethiopian Menz sheep. 2. Nitrogen metabolism. *Agroforest. Syst.* 39, 161–173.
- Kakes, P., 1991. The genetics and ecology of variation in secondary plant substances. In: Rozema, J., Verkleij, J.A.C. (Eds.), Ecological Responses to Environmental Stresses. Kluwer Academic Publishers, Dordrecht, Netherlands, pp. 234–249.
- King, D.W., Estell, R.E., Fredrickson, E.L., Havstad, K.M., Wallace, J.D., Murray, L.W., 1996a. Effects of *Flourensia cernua* ingestion on intake, digesta kinetics, and ruminal fermentation of sheep consuming tobosa. *J. Range Manage.* 49, 325–330.
- King, D.W., Fredrickson, E.L., Estell, R.E., Havstad, K.M., Wallace, J.D., Murray, L.W., 1996b. Effects of *Flourensia cernua* ingestion on nitrogen balance of sheep consuming tobosa. *J. Range Manage.* 49, 331–335.
- Lamb, J.G., Marick, P., Sorenson, J., Haley, S., Dearing, M.D., 2004. Liver biotransforming enzymes in woodrats *Neotoma stephensi* (Muridae). *Comp. Biochem. Physiol. C* 138, 195–201.
- Lamy, E., Da Costa, G., Santos, R., E Silva, F.C., Potes, J., Pereira, A., Coelho, A.V., Baptista, E.S., 2009. Sheep and goat saliva proteome analysis: a useful tool for ingestive behavior research? *Physiol. Behav.* 98, 393–401.
- Landau, S., Silanikove, N., Nitsan, Z., Barkai, D., Baram, H., Provenza, F.D., Perekovitsky, A., 2000. Short-term changes in eating patterns explain the effects of condensed tannins on feed intake in heifers. *Appl. Anim. Behav. Sci.* 69, 199–213.
- Launchbaugh, K.L., Provenza, F.D., Burritt, E.A., 1993. How herbivores track variable environments: response to variability in phytotoxins. *J. Chem. Ecol.* 19, 1047–1056.
- Lawler, I.R., Stapley, J., Foley, W.J., Eschler, B.M., 1999. Ecological example of conditioned flavor aversion in plant–herbivore interactions: effects of terpenes of *Eucalyptus* leaves on feeding by common ringtail and brushtail possums. *J. Chem. Ecol.* 25, 401–415.
- Majak, W., 2001. Review of toxic glycosides in rangeland and pasture forages. *J. Range Manage.* 54, 494–498.
- Makkar, H.P.S., Becker, K., 1998. Adaptation of cattle to tannins: role of proline-rich proteins in oak fed cattle. *Anim. Sci.* 67, 277–281.
- Malecky, M., Broudiscou, L.P., Schmidely, P., 2009. Effects of two levels of monoterpane blend on rumen fermentation, terpene and nutrient flows in the duodenum and milk production in dairy goats. *Anim. Feed Sci. Technol.* 154, 24–35.
- Mangione, A.M., Dearing, M.D., Karasov, W.H., 2004. Creosote bush (*Larrea tridentata*) resin increases water demands and reduces availability in desert woodrats (*Neotoma lepida*). *J. Chem. Ecol.* 30, 1409–1429.
- Marsh, K.J., Wallis, I.R., Andrew, R.L., Foley, W.J., 2006a. The detoxification limitation hypothesis: where did it come from and where is it going? *J. Chem. Ecol.* 32, 1247–1266.
- Marsh, K.J., Wallis, I.R., Foley, W.J., 2005. Detoxification rates constrain feeding in common brushtail possums (*Trichosurus vulpecula*). *Ecology* 86, 2946–2954.
- Marsh, K.J., Wallis, I.R., Foley, W.J., 2007. Behavioral contributions to the regulated intake of plant secondary metabolites in koalas. *Oecologia* 154, 283–290.
- Marsh, K.J., Wallis, I.R., McLean, S., Sorenson, J.S., Foley, W.J., 2006b. Conflicting demands on detoxification pathways influence how common brushtail possums choose their diets. *Ecology* 87, 2103–2112.
- Marston, A., Hostettmann, K., 1991. Plant saponins: chemistry and molluscicidal action. In: Harborne, J.B., Tomas-Barberan, F.A. (Eds.), Ecological Chemistry and Biochemistry of Plant Terpenoids. Oxford Univ. Press, New York, pp. 264–286.
- McLean, S., Duncan, A.J., 2006. Pharmacological perspectives on the detoxification of plant secondary metabolites: implications for ingestive behavior of herbivores. *J. Chem. Ecol.* 32, 1213–1228.
- Min, B.R., Barry, T.N., McNabb, W.C., Kemp, P.D., 1998. Effect of condensed tannins on the production of wool and on its processing characteristics in sheep grazing *Lotus corniculatus*. *Aust. J. Agric. Res.* 49, 597–605.
- Moore, B.D., Wallis, I.R., Paul, J.P., Brophy, J.J., Willis, R.H., Foley, W.J., 2004. Antiherbivore chemistry of *Eucalyptus*—cues and deterrents for marsupial folivores. *J. Chem. Ecol.* 30, 1743–1769.
- Mote, T.E., Villalba, J.J., Provenza, F.D., 2007. Relative availability of tannin- and terpene-containing foods affects food intake and preference by lambs. *J. Chem. Ecol.* 33, 1197–1206.
- Mote, T.E., Villalba, J.J., Provenza, F.D., 2008. Sequence of food presentation influences intake of foods containing tannins and terpenes. *Appl. Anim. Behav.* 113, 57–68.
- Mueller-Harvey, I., 2006. Unravelling the conundrum of tannins in animal nutrition and health. *J. Sci. Food Agric.* 86, 2010–2037.
- Murdiati, T.B., McSweeney, C.S., Lowry, J.B., 1992. Metabolism in sheep of gallic acid, tannic acid, and hydrolysable tannin from *Terminalia oblongata*. *Aust. J. Agric. Res.* 43, 1307–1319.
- Ngugi, R.K., Hinds, F.C., Powell, J., 1995. Mountain big sagebrush browse decreases dry matter intake, digestibility, and nutritive quality of sheep diets. *J. Range Manage.* 48, 487–492.
- Nuñez-Hernandez, G., Holechek, J.L., Wallace, J.D., Galyean, M.L., Tembo, A., Valdez, R., Cárdenas, M., 1989. Influence of native shrubs on nutritional status of goats: nitrogen retention. *J. Range Manage.* 42, 228–232.

- Oh, H.K., Sakai, T., Jones, M.B., Longhurst, W.M., 1967. Effect of various essential oils isolated from Douglas fir needles upon sheep and deer rumen microbial activity. *Appl. Microbiol.* 15, 777–784.
- Owen-Smith, N., Cooper, S.M., 1985. Classifying African savanna trees and shrubs in terms of their palatability for browsing ungulates. In: Provenza, F.D., Flinders, J.T., McArthur, E.D. (Eds.), *Proceedings of the Symposium on Plant-Herbivore Interactions*. Intermountain Research Station, Forest Service, USDA, Ogden, UT, pp. 43–47.
- Papachristou, T.G., Dziba, L.E., Villalba, J.J., Provenza, F.D., 2007. Patterns of diet mixing by sheep offered foods varying in nutrients and plant secondary compounds. *Appl. Anim. Behav. Sci.* 108, 68–80.
- Papachristou, T.G., Nastis, A.S., Mathur, R., Hutchings, M.R., 2003. Effect of physical and chemical plant defenses on herbivory: implications for Mediterranean shrubland management. *Basic Appl. Ecol.* 4, 395–403.
- Parkinson, A., Ogilvie, B.W., 2008. Biotransformation of xenobiotics. In: Klaassen, C.D. (Ed.), Casaretti and Doull's Toxicology. The Basic Science of Poisons, seventh ed. McGraw-Hill, New York, pp. 161–304.
- Perevolotsky, A., Landau, S., Silanikove, N., Provenza, F.D., 2006. Upgrading tannin-rich forages by supplementing ruminants with polyethylene glycol (PEG). In: Sandoval-Castro, C.A., Hovell, D., Torres-Acosta, J.F.J., Ayala-Burgos, A. (Eds.), *Herbivores: Assessment of Intake, Digestibility and the Roles of Secondary Compounds*. Nottingham Univ. Press, Nottingham, UK, pp. 221–233.
- Personius, T.L., Wambolt, C.L., Stephens, J.R., Kelsey, R.G., 1987. Crude terpenoid influence on mule deer preference for sagebrush. *J. Range Manage.* 40, 84–88.
- Pfister, J.A., Provenza, F.D., Manners, G.D., Gardner, D.R., Ralphs, M.H., 1997. Tall larkspur ingestion: can cattle regulate intake below toxic levels. *J. Chem. Ecol.* 23, 759–777.
- Provenza, F.D., Burritt, E.A., Perevolotsky, A., Silanikove, N., 2000. Self-regulation of intake of polyethylene glycol by sheep fed diets varying in tannin concentrations. *J. Anim. Sci.* 78, 1206–1212.
- Provenza, F.D., Malechek, J.C., 1984. Diet selection by domestic goats in relation to blackbrush twig chemistry. *J. Appl. Ecol.* 21, 831–841.
- Provenza, F.D., Pfister, J.A., Cheney, C.D., 1992. Mechanisms of learning in diet selection with reference to phytotoxicosis in herbivores. *J. Range Manage.* 45, 36–45.
- Provenza, F.D., Villalba, J.J., Haskell, J., MacAdam, J.W., Griggs, T.C., Wiedmeier, R.D., 2007. The value to herbivores of plant physical and chemical diversity in time and space. *Crop Sci.* 47, 382–398.
- Reed, J.D., 1995. Nutritional toxicology of tannins and related polyphenols in forage legumes. *J. Anim. Sci.* 73, 1516–1528.
- Riddle, R.R., Taylor Jr., C.A., Kothmann, M.M., Huston, J.E., 1996. Volatile oil contents of Ashe and redberry juniper and its relationship to preference by Angora and Spanish goats. *J. Range Manage.* 49, 35–41.
- Robbins, C.T., Mole, S., Hagerman, A.E., Hanley, T.A., 1987. Role of tannins in defending plants against ruminants: reduction in dry matter digestion? *Ecology* 68, 1606–1615.
- Rogosic, J., Estell, R.E., Ivankovic, S., Kezic, J., Razov, J., 2008. Potential mechanisms to increase shrub intake and performance of small ruminants in Mediterranean shrubby ecosystems. *Small Rumin. Res.* 74, 1–15.
- Rogosic, J., Estell, R.E., Skobic, D., Martinovic, A., Maric, S., 2006a. Role of species diversity and secondary compound complementarity on diet selection of Mediterranean shrubs by goats. *J. Chem. Ecol.* 32, 1279–1287.
- Rogosic, J., Estell, R.E., Skobic, D., Stanic, S., 2007. Influence of secondary compound complementarity and species diversity on consumption of Mediterranean shrubs by sheep. *Appl. Anim. Behav. Sci.* 107, 58–65.
- Rogosic, J., Pfister, J.A., Provenza, F.D., Grbesa, D., 2006b. Sheep and goats preference for and nutritional value of Mediterranean Maquis shrubs. *Small Rumin. Res.* 64, 169–179.
- Rogosic, J., Pfister, J.A., Provenza, F.D., Grbesa, D., 2006c. The effect of activated charcoal and number of species offered on intake of Mediterranean shrubs by sheep and goats. *Appl. Anim. Behav. Sci.* 101, 305–317.
- Salem, A.Z.M., Salem, M.Z.M., El-Adawy, M.M., Robinson, P.H., 2006. Nutritive evaluations of some browse tree foliages during the dry season: secondary compounds, feed intake and *in vivo* digestibility in sheep and goats. *Anim. Feed Sci. Technol.* 127, 251–267.
- Schwartz, C.C., Nagy, J.G., Regelin, W.L., 1980a. Juniper oil yield, terpenoid concentration, and antimicrobial effects on deer. *J. Wildl. Manage.* 44, 107–113.
- Schwartz, C.C., Regelin, W.L., Nagy, J.G., 1980b. Deer preference for juniper forage and volatile oil treated foods. *J. Wildl. Manage.* 44, 114–120.
- Shaw, R.A., Villalba, J.J., Provenza, F.D., 2006a. Resource availability and quality influence patterns of diet mixing by sheep. *J. Chem. Ecol.* 32, 1267–1278.
- Shaw, R.A., Villalba, J.J., Provenza, F.D., 2006b. Influence of stock density and rate and temporal patterns of forage allocation on the diet mixing behavior of sheep grazing sagebrush steppe. *Appl. Anim. Behav. Sci.* 100, 207–218.
- Shimada, T., 2006. Salivary proteins as a defense against dietary tannins. *J. Chem. Ecol.* 32, 1149–1163.
- Silanikove, N., Gilboa, N., Perevolotsky, A., Nitzan, Z., 1996. Goats fed tannin-containing leaves do not exhibit toxic syndromes. *Small Rumin. Res.* 21, 195–201.
- Sorensen, J.S., Dearing, M.D., 2006. Efflux transporters as a novel herbivore countermechanism to plant chemical defenses. *J. Chem. Ecol.* 32, 1181–1196.
- Sorensen, J.S., McLester, J.D., Dearing, M.D., 2005. Plant secondary metabolites compromise the energy budgets of specialist and generalist herbivores. *Ecology* 86, 125–139.
- Stolter, C., Ball, J.P., Julkunen-Tiitto, R., Lieberei, R., Ganzhorn, J.U., 2005. Winter browsing of moose on two different willow species: food selection in relation to plant chemistry and plant response. *Can. J. Zool.* 83, 807–819.
- Tellez, M.R., Estell, R.E., Fredrickson, E.L., Powell, J., Wedge, D.E., Schrader, K.K., Kobaisy, M., 2001. Extracts of *Flourensia cernua* (L.): volatile constituents and antifungal, antialgal, and antitermite bioactivities. *J. Chem. Ecol.* 27, 2263–2273.
- Utsumi, S.A., Cibils, A.F., Estell, R.E., Baker, T.T., Walker, J.W., 2010. One-seed juniper sapling use by goats in relation to stocking density and mixed grazing with sheep. *Rangel. Ecol. Manage.* 63, 373–386.
- Utsumi, S.A., Cibils, A.F., Estell, R.E., Soto-Navarro, S.A., Van Leeuwen, D., 2009. Seasonal changes in one seed juniper intake by sheep and goats in relation to protein and plant secondary metabolites. *Small Rumin. Res.* 81, 152–162.
- Villalba, J.J., Provenza, F.D., 2000. Roles of novelty, generalization, and postigestive feedback in the recognition of foods by lambs. *J. Anim. Sci.* 78, 3060–3069.
- Villalba, J.J., Provenza, F.D., 2001. Preference for polyethylene glycol by sheep fed a quebracho tannin diet. *J. Anim. Sci.* 79, 2066–2074.
- Villalba, J.J., Provenza, F.D., 2002. Polyethylene glycol influences selection of foraging location by sheep consuming quebracho tannin. *J. Anim. Sci.* 80, 1846–1851.
- Villalba, J.J., Provenza, F.D., 2005. Foraging in chemically diverse environments: energy, protein, and alternative foods influence ingestion of plant secondary metabolites by lambs. *J. Chem. Ecol.* 31, 123–138.
- Villalba, J.J., Provenza, F.D., 2007. Self-medication and homeostatic behaviour in herbivores: learning about the benefits of nature's pharmacy. *Animal* 1, 1360–1370.
- Villalba, J.J., Provenza, F.D., 2002a. Influence of macronutrients and activated charcoal on intake of sagebrush by sheep and goats. *J. Anim. Sci.* 80, 2099–2109.
- Villalba, J.J., Provenza, F.D., Banner, R.E., 2002b. Influence of macronutrients and polyethylene glycol on intake of a quebracho tannin diet by sheep and goats. *J. Anim. Sci.* 80, 3154–3164.
- Villalba, J.J., Provenza, F.D., Han, G.D., 2004. Experience influences diet mixing by herbivores: implications for plant biochemical diversity. *Oikos* 107, 100–109.
- Vourc'h, G., De Garine-Wichatitsky, M., Labbe, A., Rosolowski, D., Martin, J.L., Fritz, H., 2002. Monoterpene effect on feeding choice by deer. *J. Chem. Ecol.* 28, 2411–2427.
- Welch, B.L., McArthur, E.D., Davis, J.N., 1981. Differential preference of wintering mule deer for accessions of big sagebrush and for black sagebrush. *J. Range Manage.* 34, 409–411.
- Wiggins, N.L., McArthur, C., Davies, N.W., 2006a. Diet switching in a generalist mammalian folivore: fundamental to maximizing intake. *Oecologia* 147, 650–657.
- Wiggins, N.L., McArthur, C., Davies, N.W., McLean, S., 2006b. Spatial scale of the patchiness of plant poisons: a critical influence on foraging efficiency. *Ecology* 87, 2236–2243.
- Wiggins, N.L., McArthur, C., McLean, S., Boyle, R., 2003. Effects of two plant secondary metabolites, cineole and gallic acid, on nightly feeding patterns of the common brushtail possum. *J. Chem. Ecol.* 29, 1447–1464.
- Wink, M., 1998. Chemical ecology of alkaloids. In: Roberts, M.F., Wink, M. (Eds.), *Alkaloids: Biochemistry, Ecology, and Medicinal Applications*. Plenum Press, New York, pp. 265–300.
- Woodward, A., Coppock, D.L., 1995. Role of plant defense in the utilization of native browse in southern Ethiopia. *Agroforest. Syst.* 32, 147–161.
- Woodward, A., Reed, J.D., 1997. Nitrogen metabolism of sheep and goats consuming *Acacia brevispica* and *Sesbania sesban*. *J. Anim. Sci.* 75, 1130–1139.