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Review: Herbivory and the power of phytochemical diversity on animal health

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ABSTRACT

Plant secondary compounds (**PSCs**) were thought to be waste products of plant metabolism when first identified in the mid-1800 s. Since then, many different roles have been recognized for these chemicals. With regard to their function as defense, PSCs can negatively impact different cellular and metabolic processes in the herbivore, causing illness and reductions in feed intake. This penalty on fitness also applies to other trophic levels, like the microorganisms and parasites that infect herbivores and thus, PSCs at certain doses may function as medicines. In turn, herbivores evolved learning mechanisms to cope with the constant variability in their environment and physiological needs. Under this context, foraging can be viewed as the quest for substances in the external environment that provide homeostatic utility to the animal. For instance, herbivores increase preference for PSC-containing feeds that negatively impact infectious agents (i.e., therapeutic self-medication). Given that some classes of PSCs like polyphenols present antioxidant, antiinflammatory, immunomodulatory and prebiotic properties, chronic and sustained consumption of these chemicals results in robust animals that are tolerant to disease (i.e., prophylactic self-medication). Foraging plasticity in terms of the quality and quantity of nutrients ingested in the absence and during sickness may also influence immunocompetence, resistance and resilience to infection, and thus can be interpreted as another form of medication. Finally, self-medicative behaviors can be transmitted through social learning. We suggest that foraging studies will benefit from exploring self-medicative behaviors in chemically diverse plant communities, in particular when considering the vast diversity of PSC structures (more than 200 000) observed in nature. We then lay out a framework for enhancing the medicinal effects of PSCs on grazing herbivores. We propose landscape interventions through the establishment of resource patches or "islands" with a diversity of PSC-containing forages (e.g., legumes, herbs, shrubs) in monotonous rangelands or pasturelands, viewed as a "sea" of low-diversity vegetation devoid of functional biochemicals. Strategies aimed at enhancing the diversity of plant communities lead to heterogeneity in chemical, structural and functional landscape traits that offer options to foragers, and thus allow for balanced diets that maintain and restore health. Beyond animal health, such heterogeneity promotes a broad array of ecosystem services that significantly improve landscape resilience to environmental disturbances.

Implications

Multiple therapeutic and prophylactic functions are being revealed for plant biochemicals. Understanding the drivers of the ingestive behavior of herbivores when presented with these compounds, coupled with the strategic spatial distribution of medicinal plants in the landscape will create sustainable approaches for the treatment and prevention of disease. In addition to enhancing animal health, these interventions have the potential to improve other ecosystem services like clean air, improved soil quality, wildlife and pollinator habitat.

Introduction

Rangelands and pasturelands provide herbage for ruminant production systems worldwide and are a source of high-quality edible protein and cash income from non-arable lands (Varijakshapanicker et al., 2019; Adesogan et al., 2020). Under this context, producers are challenged to maintain profitable operations while addressing growing consumer demands for environmentally, economically, and socially sustainable food (Sanderson

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et al., 2007; Villalba et al., 2019). Historically, cattle evolved in the Mediterranean region grazing a diverse palette of herb, shrub and grass species (Grove and Rackham, 2001), but livestock grazing rangelands and pasturelands today consume a diet dominated by grasses from improved species in monocultures and even solid monospecific weed stands that invade degraded landscapes (Paterson et al., 2001; Robins et al., 2020). In addition to the declining nutritional value of these forages as they mature, monoculture grass diets are typically devoid of functional doses of plant secondary compounds (**PSCs**) that are significant for animal health and the neutraceutical properties of their products (e.g., meat and milk) (Van Vliet et al., 2021; 2023).

Plant secondary compounds, such as phenolics, terpenoids and alkaloids, are chemicals generally present in woody species, legumes and herbs. These compounds were long regarded as waste products of plant metabolism, ever since they were identified in the second half of the 19th century (Hartmann, 2008). Since then, many different roles have been recognized for PSCs, including their indispensable involvement in the survival strategies of plants (Hartmann, 2007), most notably as plant defense against herbivores (Palo and Robbins, 1991). More recently, this vast array of compounds involving more than 200 000 defined chemical structures, have been linked to many regulatory functions for the primary metabolism of plants (Erb and Kliebenstein, 2020). With regard to their role as chemical defenses, PSCs restrict the amount of plant tissue lost to herbivores through their negative postingestive actions at different cellular and metabolic levels, causing tissue and metabolic damage, reductions in feed intake, digestibility, weight gains and potentially death (Cheeke and Shull, 1985; Robbins et al., 1987).

Mammalian herbivores learn to associate the postingestive consequences of eating a specific food with its orosensorial properties (Provenza, 1995), and excesses of PSCs in foods (or excesses of nutrients) cause food avoidance as high concentrations of these chemicals in the animal's body cause toxicity and malaise (Provenza et al., 2003). Ingestion of PSCs can cause dose-dependent decreases in food intake (Dziba and Provenza, 2008), but not all biological activity associated with PSCs is negative; PSC consumption has also been associated with a range of medicinal properties (Athanasiadou et al., 2007; Tolossa et al., 2013). Thus, ruminants develop preferences for the flavors of food associated with the provision of needed nutrients and medicinal PSCs (Villalba and Provenza, 1997a,b,c; Villalba et al., 2014). This entails a dual action for nutrients and PSCs on animals, from toxic to beneficial depending on dose and the temporal and spatial context where such chemicals were ingested (Provenza et al., 2003). Mammalian herbivores, through the behavioral adaptation of their diet selection, can control the intake of PSCs to their benefit. In that respect, a unifying and dynamic framework –behavior by consequences – is initially presented in this review to set the underpinning principles that explain the flexibility and adaptability of mammalian herbivores to the selection of chemicals in plants. Subsequently, the medicinal and prophylactic properties of PSCs are discussed and integrated with the foraging responses of herbivores to such chemicals. Finally, a framework is proposed for devising landscape interventions aimed at enhancing animal health through increments in the taxonomic and chemical diversity of grazing lands. A preliminary analysis has been presented at the 11th International Symposium on the Nutrition of Herbivores and published in abstract form (Villalba, 2023).

Behavior by consequences paradigm: homeostatic endeavor and food selection in mammalian herbivores

Plasticity in diet selection is essential in allowing herbivores to adapt to feeding environments that change in time and space and to fluctuations in their internal state. It is not enough for animals to have specific and static avoidances for the taste of PSC-containing foods or fixed preferences for the taste of nutritious foods, or even a taste system that just discriminates nutrients from PSCs. In order to maintain the biochemical welfare of the species, the organization of the food selection process must be plastic (Provenza et al., 2003; Scott, 2011). In this regard, herbivores evolved learning mechanisms to cope with the frequent changes occurring in their internal and external environment. To survive in a world where these environments change constantly requires that individuals experience the consequences of their actions (Provenza, 1995). In order for this process to evolve, constant monitoring of the animal's internal state and ongoing changes in behavior are required, in ways that sensorial inputs and metabolic processes are integrated with experiences of pleasure and pain, incentive motivation, and feelings (Damasio, 2003). A monitoring system (i.e., that includes receptors) is key because behaviors at all levels, from cells and organs, to social and biophysical environments, contribute to drive the body toward a dynamic state of homeostasis (Rose, 1997). This self-regulatory dynamic state of equilibrium has been coined as "homeodynamics" in an attempt to represent the inherent adaptive response of all living organisms at maintaining internal constancy and stability – conditions necessary for life – while living in an interconnected and dynamic open system far from equilibrium. Thus, the view of a self-organizing and dynamic living state emerges, not just as a linear adaptation to a changing external world but as an integration with internal fluctuations in physiological organization and set points that occur throughout the lifetime of the individual (Rose, 1997; 1999). From this perspective, behavior can be interpreted as a key action that contributes to drive organisms to an homeodynamic state, given that behavior is a function of its consequences, which in turn change the likelihood of future behaviors (Skinner, 1984). In the case of foraging, behavior by consequences is manifest as the interrelationship between a preference (behavior) for a food's flavor and its postingestive effects (Provenza, 1995). Flavor is the integration of odor, taste, and texture with postingestive feedback emanating from cells and organs caused by the ingestion of a food, which provide different types and concentrations of biochemicals to the internal environment (Provenza, 1995). The senses of smell, taste, and sight enable animals to discriminate among foods and provide sensations – like or dislike for a food's flavor – associated with eating. In turn, postingestive feedback calibrates sensory experiences as a function of the food's homeostatic utility to the individual (Provenza and Villalba, 2006). Thus, flavor-feedback interactions emerge from an animal's physiological state and a food's biochemical and sensorial characteristics. In turn, postingestive feedback affects liking for flavor (palatability) as a function of physiological needs and past experiences with food (Provenza et al., 2003; Provenza and Villalba, 2006).

In the case of flavor-feedback interactions, afferent neurons from the taste system converge in the brain stem with neurons carrying sensorial information from the gastrointestinal tract, and then, they synapse and relay information to the limbic system and then to the cortex in the central nervous system influencing behavior (Ran et al., 2022; Watts et al., 2022). Feedback from physiological sensations in the internal environment to the taste system is how cells and organs influence which foods, and how much of those foods, are consumed by an animal. Thus, the taste system manages foraging behavior by qualitatively and quantitatively analyzing foods in concert with afferent sensorial information gathered from the gastrointestinal tract, all of which evoke current and past experiences with food (Provenza et al., 2003; Provenza and Villalba, 2006; Scott, 2011). It should be noted that taste reception is located at the junction between the internal environment and the outside world, like a Janus head placed at the gateway to the body, one face looking at what is outside and acting as the gate keeper, i.e., allows or rejects the access of food, and the other face looking at what is inside the organism and relying this information (postingestive feedback) to the gate keeper (Scott, 1990; Provenza and Villalba, 2006). This system is key from an evolutionary standpoint, given that the average lifetime of a species is several million years (Toljagić et al., 2018; Chen et al., 2019) and the types and diversity of feeds herbivores are likely to encounter are highly variable over such time period (Futuyma and Agrawal, 2009). Learning by consequences is itself a genetically evolved mechanism, a type of fixed plasticity that, like evolution, is adaptive (Skinner, 1984; Martina et al., 2020).

Under the behavior by consequences paradigm, lambs learn to prefer flavors associated with intraruminal infusions of starch, volatile fatty acids, protein, and minerals, chemicals that contribute to satisfy the animals' requirements and thus provide an homeostatic utility to the individual (Villalba and Provenza, 1997a,b,c; Villalba et al., 2008). On the other side of the flavor-postingestive feedback continuum, the seminal work by Provenza et al. (1990) showed that goats learned to avoid a condensed tannin (**CT**)-containing shrub (*Coleogyne ramosissima*) by associating the flavor of this plant with aversive postingestive consequences (i.e., deviations from homeostasis) triggered by CT, a PSC. How PSCs are affecting foraging responses in diseased and healthy herbivores is discussed in the next sections.

Plant secondary compounds, health status and foraging responses in herbivores

The negative impacts for PSCs described above for herbivores, also apply to other trophic levels, such as the microorganisms and parasites that infect herbivores' bodies causing sickness (Lozano, 1998). For instance, forage-derived alkaloids, terpenes and phenolics consumed at appropriate doses have antiparasitic, antibacterial, antifungal and antiviral properties (Copani et al., 2013; Hoste et al., 2015; Mueller-Harvey et al., 2019; Mohan et al., 2020; Redondo-Blanco et al., 2020; Stapleton et al., 2022). It is known that CT, a vast array of polyphenols, can have potent, direct anthelmintic effects that cause severe structural alterations in the worms which impair their motility, nutrition and reproduction (Athanasiadou and Kyriazakis, 2004; Hoste et al, 2006; Martínez-Ortíz-de-Montellano et al., 2013). Such direct effects cause a reduction of migratory ability of newly hatched larvae, lower establishment of the infective third-stage larvae (**L3**) in the host, lower excretion of eggs by adult worms, and impaired development of eggs into L3 (Hoste et al., 2015; Chylinski et al, 2023), all mechanisms that contribute to restore herbivore health. Likewise, terpenoids inhibit efflux pumps in pathogenic bacteria (Dias et al., 2022), and plant phenolics and alkaloids disrupt bacterial membranes, interfere with bacterial DNA structure and inhibit bacterial enzymes, all causing antibiotic actions (Cushnie et al., 2014; Rempe et al., 2017). Consistent with this, plant phenolics (cinnamic and ellagic acids) show antibiotic activity against enteropathogenic *Escherichia coli* (O157:H7) (Shamansoori et al., 2022). Likewise, PSCs like flavonoids and terpenoids disrupt the integrity of fungal cell membranes, leading to leakage of intracellular components and cell death; they also inhibit cell wall formation, mitochondrial electron transport chain, cell division, RNA/DNA synthesis or protein synthesis, and efflux pumps in fungal cells (Lagrouh, et al., 2017; Zaynab et al., 2018; Al Aboody and Mickymaray, 2020). In turn, PSCs (e.g., flavonoids, alkaloids, terpenoids) also promote antiviral actions, from negatively impacting viral entry, viral DNA and RNA synthesis, or viral development and replication in cells (Ghildiyal et al., 2020; Wink, 2020).

The same flavor-postingestive feedback mechanism underlying preference (behavior) for foods and flavors associated with nutrients that drive organisms to a dynamic homeostatic state (consequences) also explains preferences for some PSC-containing feeds by sick herbivores: Ingestion of certain medicinal bioactives at appropriate doses negatively impact pathogens and contribute to restore health (Huffman et al., 2020). The idea that animals could consume substances that were associated with recuperation from illness was first shown in an experiment by Green and Garcia (1971), where rats received a distinctive flavor during recuperation (i.e., through detoxification and elimination) from injection of a noxious drug. Subjects showed a clear preference for the flavor conditionally paired with such recovery, which was attributed to a positive "medicinal" effect, independent of novelty or initial preference, and thus learned (Green and Garcia, 1971). Following this key finding, the idea that animals could ingest plants in the wild as a function of their medicinal value was proposed by Janzen (1978), rooted on a diversity of anecdotal observations. Subsequently, the seminal work in the African great apes starting in the mid-to-late 1980 s revealed the key roles of certain learned behaviors (i.e., chewing on bitter bioactive-containing plants and leaf swallowing) in the control of intestinal parasites and relief from gastrointestinal upset (see Huffman, 1997; 2003; 2015; Huffman et al., 2020; Freymann et al., 2024).

With regard to domestic ruminants, parasitized lambs with *Haemonchus contortus* showed a greater preference for tannin-containing foods and forages than non-parasitized animals, and these differences in preference disappeared when parasite loads were eliminated by chemotherapy, suggesting ruminants can learn to self-medicate (Juhnke et al., 2012; Villalba et al., 2014). Associative individual learning is essential for this behavior, as only sheep experiencing the association medicine-relief from illness acquire a preference for the medicine (Villalba and Provenza, 2001; 2002). Naïve sick lambs that do not experience such association are unable to prefer medicines that counter specific negative internal states like toxicity from experimentally applied dietary toxins or caused by haemonchosis (Villalba et al., 2006; Juhnke et al., 2012). Moreover, self-medicative behaviors are not observed when the medicine is familiar but ingested only when the animal is healthy, or when the medicine is highly available; the individual needs to experience the association between ingesting a medicine followed by relief from illness (Villalba and Provenza, 2001; 2002; Juhnke et al., 2012). Likewise, Mamber goats learn to increase their intake of and preference for *Pistacia lentiscus,* a medicinal tannin-containing shrub, only when experiencing relief from being infected with the gastrointestinal nematode *Haemonchus contortus* (Amit et al., 2013). On the other hand, studies with infected criollo goats browsing in a tropical deciduous forest with tannin-rich vegetation have not been able to identify therapeutic self-medicative behaviors (Ventura-Cordero et al., 2017; Novelo-Chi et al., 2019). Thus, other variables in such ecosystem appear to influence foraging behavior to a greater extent than the selection of condensed tannins as a function of infection. In addition to ruminants, a variety of animals have been reported to engage in self-medicative behaviors through the ingestion of a PSC that negatively impacts infection, from the described research on apes (Huffman, 1997; Huffman and Hirata, 2004) to insects (Singer et al., 2014, de Roode and Hunter, 2019). Moreover, some of these behaviors observed in nature have represented a fundamental source of knowledge about the use of medicinal plants by humans (Álvaro et al., 2019; Huffman, 2022).

Although associative learning has been demonstrated in insects (Moore et al., 2013), self-medication may not necessarily entail an associative learning process for these individuals, but rather an innate response (de Roode et al., 2013). Consistent with this idea, gustatory cells in parasitized caterpillars fire action potentials more rapidly than those in unparasitized individuals in response to pyrrolizidine alkaloids (**PA**), a group of PSCs with antiparasitic actions (Bernays and Singer, 2005). This specific change in gustation leads to greater intakes of medicinal PA in parasitized than in non-infected individuals, which leads to greater survival rates than in parasitized caterpillars with no access to PA (Singer et al., 2009). This response has been explained through plasticity in the peripheral nervous system of caterpillars, without the intervention of associative learning (Singer et al., 2009; 2014). Parasitized caterpillars sense the presence of internal parasites, chemically signaling the taste system, which in turn reduces the threshold of tolerance to toxic but medicinal PSCs (Singer et al., 2009). Despite the different origins of the self-medicative response, the process described here still fits the idea of homeostatic endeavor and homeodynamics in living organisms: An adaptive behavior triggered by an internal detection system that monitors a deviation from homeostasis caused, in this case, by a parasite.

Consistent with the aforementioned dynamic flexibility of taste responses in insects, mammalian herbivores may also display increases in the acceptance of PSCs when experiencing illness (Poli et al., 2018), particularly when analyzing responses to bitter-tasting compounds, a sensorial dimension linked to toxins and typically disliked and avoided by animals (Glendinning, 1994; Pass and Foley, 2000). Several bioactive compounds with antimicrobial or antiparasitic activity taste bitter (Koshimizu et al., 1994; Cavallo et al., 2019), and thus the risk-prone behavior by sick individuals of increasing the intake of potentially toxic bitter feeds enhances the likelihood of ingesting therapeutic doses of PSCs. After experiencing the positive consequences of an increased consumption of bitter PSCs (i.e., recuperation from illness), associative learning may complement the response as described before. Thus, an increased acceptance to bitter-tasting compounds during sickness may enhance the likelihood of medication and individual learning. In support of this idea, naïve parasitized lambs showed greater acceptance of bitter tannin-containing feeds (Lisonbee et al., 2009), and they displayed a greater preference for a ration containing bitter-tasting antioxidant polyphenols and terpenes than healthy individuals (Poli et al., 2018). Moreover, parasitized lambs accepted novel feeds and flavors more readily than non-parasitized controls, suggesting a risk-prone behavior in response to a parasitic infection, which allows for a greater likelihood of ingesting medicinal foods at appropriate doses (Egea et al., 2014).

Many medicinal plants taste bitter, suggesting that bitterness is a signal of therapeutic value to animals just as it is for humans (Wooding et al., 2021), reinforcing the idea of an increased acceptance for bitter in infected individuals and the concomitant effectiveness for the dose ingested. Under this scenario, it has been hypothesized that bitter perceptions co-evolved with society habits and environment in humans (Krebs, 2009). For instance, populations living in regions where malaria, a parasitic disease, was endemic might have benefited by their high tolerance to plant-derived bitter compounds (e.g., quinine) which are therapeutic against malaria (Soranzo et al., 2005; Krebs, 2009). On the other hand, some proinflammatory signaling factors such as tumor necrosis factor-α (**TNF-α**) have their receptors expressed in taste buds, linking inflammation with taste function and food intake (Goodman and Dando, 2021). It has been found that TNF-α knock out mice are less sensitive to bitter flavors than wild−type mice (Feng et al., 2015), suggesting that inflammation may contribute to reduce, instead of enhance, acceptance of bitter taste in mammals. Nevertheless, more research is needed on this topic as it is possible that TNF-α knock−out mice are inherently more tolerant to bitter flavors due to developmental abnormalities (Rogers, 2015).

Trade-offs between medicinal and toxic effects of plant secondary compounds

Therapeutic self-medication can be interpreted as an induced, adaptive behavioral response to sickness through the increased consumption of a bioactive PSC that restores health. Nevertheless, bioactive PSCs are allelochemicals that at therapeutic doses may also impinge multiple deleterious effects to the host given their role as chemical defenses (Palo and Robbins, 1991). Thus, therapeutic self-medication can be considered adaptive when there is a detectable threat to the host (i.e., an infection), but it may entail a fitness cost when the animal is healthy (Singer et al., 2009). From this perspective, therapeutic self-medication can be viewed as a type of adaptive plasticity in animals, where the behavior −triggered by sickness- improves fitness in sick animals, but it is costly and decreases fitness in healthy individuals (Singer et al., 2009). In summary, therapeutic self-medication is likely to occur when the risks and costs promoted by the infection are high relative to the costs and risk of consuming a toxic medicine (de Roode and Hunter, 2019). Consistent with this, it has been proposed that in order to identify self-medicative behaviors in the wild, animals should show signs of being ill, seek out and consume substances that are not part of the normal diet, with enough concentration of bioactives that lead to an improvement in health (Huffman, 2003). This analysis suggests infected herbivores are balancing the costs of PSC intake with the benefits brought about by recovery and the potential additional costs of greater levels of infection that the animal would have incurred if lower to nil amounts of PSCs were consumed (Hutchings et al., 2006).

One way of increasing the benefits of PSC consumption over the costs of ingesting a toxin may be detoxification, coupled with the temporal pattern at which PSCs are ingested. Foragers could maximize a medicinal dose at certain times, while allowing other times for detoxification, when nil to low doses of medicine are ingested. In this regard, wild chimps ingest the pith from young shoots of the medicinal plant *Vernonia amygdalina* only when infected with gastrointestinal parasites, and for specific periods within a season, despite the fact that the plant is highly available year-round, with subsequent clear reductions in parasitic burdens (Huffman, 2015). The pith from *Vernonia amygdalina* shoots is extremely bitter, containing sesquiterpene lactones and glycosides that are antiparasitic, but also very toxic to chimps (Koshimizu et al., 1994). Bitter pith chewing has been observed to occur on a certain day; individuals are not seen to eat the plant again within the same day or even within the same week (Huffman, 2016). Likewise, parasitized lambs consume antiparasitic tannin-containing food in pulses, with peaks during some days (when the dose of the medicine is maximized) and low to nil consumption of medicine during other days (when the animal allows for detoxification and elimination of the medicine consumed), a sawtooth feeding pattern that was effective at reducing parasitic loads (Juhnke et al., 2012). Limits on intake are set by the rates at which PSCs can be eliminated from the body (Foley and McArthur, 1994). At certain thresholds, PSCs saturate the detoxification capabilities of herbivores (Provenza et al., 2003). At these levels, animals quit feeding, and they resume eating only after PSC concentrations in the body decline due to detoxification and elimination processes (Pfister et al., 1997; Foley et al., 1999). This mechanism causes cyclic patterns of feeding with peak intakes at the lowest concentration of PSCs in the body (Pfister et al., 1997; Foley et al., 1999).

Detoxification of dietary PSCs is not only directly encoded in herbivore genomes, i.e., cytochrome P450 enzymes in liver, kidney or lung (Cheeke and Shull, 1985; McLean and Duncan, 2006). Mounting evidence suggests that the gut microbiota has the potential to detoxify PSCs, allowing for a greater adaptation to PSC-containing diets (Dearing et al., 2022; Stapleton, 2022). Thus, ruminal and colonic microbes, which are in turn influenced by diet (Youngblut et al., 2019; Zhu et al., 2021) can modulate the penalties imposed by PSCs in self-medicative responses. This, in turn, has different implications for foregut and hindgut fermenters (Dearing and Weinstein, 2022). More research is needed to analyze the costs of ingesting toxic medicines not only by taking into consideration the involvement of detoxifying mechanisms from the host but also the role of symbionts at mediating detoxification by herbivores.

Nutritional self-medication

A shift in macronutrient intake by sick individuals during the foraging process has been interpreted as nutritional self-medication against infection (Ponton et al., 2020). This is because many bacterial, viral and parasitic infections promote significant nutrient loses, as well as reductions in voluntary food intake by the host (Kyriazakis et al., 1998). In addition, ingestion of medicinal PSCs imposes constraints on nutrient intake, dilutes dietary nutrients (Villalba et al., 2017), and causes nutritional costs triggered by detoxification (Illius and Jessop, 1995; Foley et al., 1999; Au et al., 2013). Finally, immunological processes caused by infection compete for the same physiological resources needed to be partitioned into vital functions such as maintenance and growth, thus causing trade-offs in nutrient allocation (Kyriazakis and Houdijk, 2006; Singer et al., 2014). Under this scenario, sick foragers may modify the proportion of nutrients selected, even when constrained by the total amount of feed they can ingest. For instance, parasitized (*Haemonchus contortus*) lambs that learned to self-medicate and offered choices between tannin- and non-tannin–containing rations, traded-off a greater content of tannins with a lower content of CP in their diet than naïve parasitized or healthy control animals, but with similar amounts of digestible energy ingested (Villalba et al., 2017). Thus, in these studies, sick sheep appeared to “defend” their intake of digestible energy while allowing for a lower intake of CP, which was traded off for a greater intake of medicinal PSCs (Villalba et al., 2017). Likewise, groups of parasitized lambs (*Haemonchus contortus*) that could choose between foods of high or low energy–to–protein ratios, or the same choice with added (4%) Quebracho tannins in either or both foods, prioritized the ingestion of energy-dense over protein-dense feeds (Costes-Thiré et al., 2019). Under this feeding context, parasitized lambs prioritized intake of digestible energy while medicinal tannin intake represented a side-effect of the preference manifested for energy-dense foods, likely to satisfy requirements triggered by growth and parasitism (Costes-Thiré et al., 2019).

Some research also suggests increased supply of protein, instead of energy, contributes to reduce gastrointestinal nematode parasitism (e.g., *Trichostrongylus colubriformis*; *Haemonchus contortus*) in sheep (Coop and Kyriazakis, 1999; Kyriazakis and Houdijk, 2006), as such infections promote significant losses of endogenous protein into the gastrointestinal tract (Holmes, 1993). In addition, the protein required to be partitioned into productive functions competes with protein needed for the acquisition and expression of immunity (Kyriazakis and Houdijk, 2006). However, some studies show no improvements in parasitic resilience followed by increased protein intake (e.g., Coop et al., 1995). It is likely that in some studies, energy supply and not protein is the key limiting nutritional factor, or that the availability of certain specific amino acids (e.g., methionine, one of the first limiting amino acids in microbial protein (Merchen and Titgemeyer, 1992); tryptophan, involved in several key physiological processes like neuronal function, immunity, and gut health (Comai et al., 2020)) is more significant than the total amount of protein available in the diet *per se* (Coop and Kyriazakis, 1999). In fact, PSCs like CT protect proteins from degradation in the rumen, thus increasing the availability of dietary protein to the intestine, potentially increasing the supply of limiting amino acids like methionine to the host (McNabbl et al., 1993). Moreover, it has been suggested that infected goats (*Haemonchus contortus*) offered foliage of five plant species with a decreasing gradient of condensed tannin concentration, prioritized ingestion of tannin-rich forages to prevent rumen proteolysis and thus reduce energy losses due to urea urinary excretion (Ventura-Cordero et al., 2018).

With regard to the amount of food consumed, compensatory feeding has been defined as a behavior which allows animals to make up for nutritional losses caused by infection. Compensatory feeding has not been regarded as therapeutic because the extra nutrients ingested are not necessarily used to eliminate or suppress the pathogen, just to cope with or restore the deficiencies caused by the infection (Shikano and Cory, 2016), or because the behavior does not necessarily confer fitness costs to uninfected individuals (Abbott, 2014). Parasitized lambs offered choices between antiparasitic tannin- or saponin-containing feeds, which enhanced their overall feed intake relative to parasitized individuals offered just one of the PSC-containing feeds (Copani et al., 2013). This increased intake by animals given a choice is explained through the toxin dilution hypothesis, stating that food mixing allows herbivores to avoid ingesting toxic doses of the particular PSCs characteristic of specific single foods (Freeland and Janzen, 1974). The dietary decision by parasitized lambs offered a 2-way choice entailed harvesting more feed, and thus more protein and digestible energy and lower doses of total PSCs than animals with no choice, fed either tannin- or saponin-containing foods. However, lower total doses of PSCs ingested by animals offered choices that led to greater parasitic loads. Nevertheless, this decision paid off as animals offered a choice ingested more nutrients and showed a better performance than animals fed single PSCs (Copani et al., 2013).

Fruit flies (*Drosophila melanogaster*) infected by a pathogenic bacterium also “defend” their energy intake by maintaining carbohydrate intake while reducing their protein intake relative to uninfected individuals, a behavior that reduces the proportion of dying flies to the infection (Ponton et al., 2020). This change in diet selection by infected flies has been linked to an upregulation in the expression of constitutive immune genes coding for antimicrobial peptides (Ponton et al., 2020). In contrast to the fruit fly, parasite-challenged caterpillars self-medicate by increasing their dietary intake of protein relative to carbohydrate (Shikano and Cory, 2016). Such nutrient compensation can help combat disease and eliminate pathogens via aiding the immune response. In this case, the increase in the intake of protein relative to controls and subjects dying of infection leads to the benefit of an improved constitutive immune function (Lee et al., 2006), which increases the likelihood of clearing pathogens before they start replicating and establishing inside the host. Likewise, parasitized sheep and goats given choices among foods of different nutrient densities select a diet of higher protein content than non-parasitized animals, which allows for an improvement in resilience and resistance to parasitic infection (Kyriazakis et al., 1994, 1996). Collectively, these scenarios show that in addition to ingesting PSCs detrimental to the infectious agent, there are alternative adaptive decisions like changes in dietary quality or quantity which also contribute to the overall fitness of the individual (Bernardo and Singer, 2017).

Prophylactic effects of plant secondary compounds and self-medication

In addition to their direct negative impacts on parasites and microorganisms, plant bioactives may have other beneficial effects to herbivores in the absence of any specific pathogens, through their antioxidant, prebiotic, antiinflammatory or immunomodulatory properties. For instance, sustained consumption of low doses of plant-derived phenolics, terpenes, flavonoids, and volatile oils have been found to attenuate inflammation and oxidative stress in farm animals, which collectively promote positive effects on performance, health, and product quality (Gessner et al., 2017; Tsiplakou et al., 2021; Nehme et al., 2021). The importance of sustained availability of dietary bioactives for reducing oxidative stress (Hao et al., 2020) and inflammation (Jaiswal et al., 2020), and for enhancing immunocompetence (Oh and Hristov, 2016) is becoming evident in ruminant animals. In addition, plant polyphenols at appropriate levels have been shown to interact with the gut microbiota, maintaining a balance in its microbial community and promoting prebiotic benefits with impact on gut health (Molino et al., 2021; Redondo et al., 2022). Finally, it has been hypothesized that goats browsing tropical deciduous forest tend to favor a prophylactic strategy of medication, given that bioactives in those forages reduce the establishment of larvae in the gastrointestinal tract, i.e., by blocking the exsheathment of infective larvae, limiting the size and fecundity of adult worm females, or reducing the viability of eggs (Torres-Fajardo et al., 2019; 2024).

Mechanisms of action known for plant secondary compounds

Like in plants, antioxidants (e.g., polyphenols, carotenoids) consumed with diet reduce oxidative stress by scavenging reactive oxygen species that cause oxidative damage to DNA, proteins, or lipids in animal cells (Finkel and Holbrook, 2000; Monaghan et al., 2009; Gessner et al., 2017). Polyphenols also induce the expression of antioxidant/phase II enzymes in mammals, and function as modifiers of signal transduction pathways that elicit cytoprotective responses to oxidative damage (Lee et al., 2017a). On the other hand, not all plant polyphenols are strong antioxidants and they can even act as pro-oxidants (Sakihama et al., 2002; Salminen and Karonen, 2011). Antiinflammatory functions of PSCs like polyphenols are intertwined with their antioxidant effects, as their antioxidant function at cellular and molecular levels influences the expression of pro-inflammatory genes, and the regulation of inflammatory signaling (Yahfoufi et al., 2018). Polyphenols, triterpenoids and stilbenes inhibit protein kinase C and mitogen-activated protein kinase in mammalian cells by altering the DNA-binding capacities of transcription factors such as nuclear factor kappa-B (**NF-κB**), a pivotal mediator of inflammatory responses (Liu et al., 2017). These PSCs also inhibit the overproduction of inflammatory mediators, like pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and TNF-α, and they down-regulate inducible nitric oxide synthase, cyclooxygenase-2, and reactive C-protein, all key mediators and enzymes of the inflammatory response (Zhu et al., 2018).

In addition to their antioxidant activity, PSC can affect immune responses. For example, polyphenols and essential oils are PSCs with evidence for immunomodulatory activity (Williams et al, 2020). Human studies have demonstrated that polyphenols can reduce overexpression of T-helper (Th)-1 and Th17, immune responses that may drive the immunopathology associated with intestinal inflammation (Yoshioka et al., 2008). They have also been shown to enhance the production of anti-inflammatory cytokines and mucosal antibodies (Pierre et al., 2013; Denis et al., 2015). Polyphenols and carotenoids enhance immunity by supporting the proliferation of lymphocytes and aggregation of platelets. They also increase natural killer-NK cell activity, phagocytosis, and stimulate the secretion of antibodies (Maheshwari et al., 2022). Condensed tannins, which are polymers of flavonoid units, have been shown to reduce gastrointestinal nematode burden and boost immune responses when consumed by infected herbivores. A reduction in the level of gastrointestinal nematode infections in small ruminants (Athanasiadou et al., 2000, 2001; Paolini et al., 2003a, 2005; Marley et al., 2006; Niezen et al., 2002) could also be attributed to enhanced immunity triggered by condensed tannin intake. For instance, an increase in the number of small intestinal mucosal mast cells (implicated in the expulsion of nematodes from the gastrointestinal tract) has been reported in goats receiving condensed tannin extracts representing 5% of the diet (Paolini et al., 2003a). Nevertheless, the same extracts did not influence the number of abomasal mast cells in parasitized sheep (Paolini et al., 2003b) or the level of abomasal infection (Athanasiadou et al., 2001). It is likely that there is a reduction in the bioavailability of condensed tannins in the abomasum, given that these compounds may be bound to other macromolecules that prevent their immunomodulatory or antiparasitic activities (Mueller-Harvey, 2006). A change in pH and the presence of other compounds in the small intestine such as surfactants may create the appropriate medium conditions to promote a dissociation from those macromolecules, thus restoring the bioactivity of contended tannins at the intestinal level. In addition, the biological activities of phenolic compounds are mediated by their metabolites with antioxidant and antiinflammatory properties, produced from their parent compounds through metabolic processes in the liver, intestine and microbiota (Di Lorenzo et al., 2021).

The effects of condensed tannins have also been explored under grazing conditions, when infected animals graze tannin-rich forages and the results are contrasted against those grazing control pastures without tannins. Several condensed tannins, flavonoids and saponins have been identified in the legume sulla (*Hedysarum coronarium*) (Tava et al., 2021; Molinu et al., 2023), and parasitized sheep grazing this plant have shown increments in the number of abomasal mucosal mast cells, globule leukocytes, and in antibody titers against parasite antigens relative to animals grazing control grass/legume pastures (Niezen et al., 2002; Tzamaloukas et al., 2006). Likewise, sheep grazing the condensed tannin-rich legume sainfoin (*Onobrychis viciifolia*) (Wang et al., 2015) showed increments (relative to animals grazing control pastures without condensed tannins) in the intestinal concentrations of mucosal eosinophils, mast cells, and Paneth cells, all cell types involved in intestinal immunity (Rıos-de Alvarez et al., 2008). Nevertheless, it is likely that the aforementioned immunomodulatory responses were not only influenced by the direct effects of condensed tannins. These chemicals also form stable complexes with dietary proteins in the rumen, preventing their proteolysis and thus allowing for a greater availability of high-quality dietary protein at the intestinal level (Min and Hart, 2003), which in turn may exert immunomodulatory effects (Athanasiadou and Houdijk, 2010).

Herbivores can combat the impact of infections through mechanisms of tolerance, which entail fitness maintenance without necessarily reducing the level of infection (Schneider and Ayres, 2008). Although there is not much evidence on the impact of PSC on tolerance mechanisms, one recent study by Blomstrand (2022) demonstrated that administration of tree bark extracts rich in CT resulted in an improvement in tolerance of mice susceptible to the intestinal nematode *Heligmosomoides bakeri*, whereas there was no impact in the tolerance of resistant mice. This effect was evident in the absence of a clear anthelmintic effect from the CTs in the bark and demonstrates that certain PSCs can have a beneficial effect on the performance of infected animals, and influence their ability to withstand the impact of an infection, without affecting pathogen load.

Finally, some PSC and polyphenols, in particular, can modify the composition of the intestinal microbiome through selective stimulation or inhibition of different microbial communities. These effects could be explained through their selective antibiotic effects or to prebiotic effects mediated by the production of autoinducers, with the potential to improve gut and overall animal health (Santhiravel et al., 2022). For instance, a blend of tannin extracts given to humans promoted an increase in colonic microbial diversity, with increments in the relative abundances of several beneficial taxa, some responsible for an increase in the production of microbial metabolites – short-chain fatty acids- that contribute to the modulation of the immune system with several anti-inflammatory functions in the gut (Molino et al., 2022). Supplementing Holstein calves with green tea polyphenols promoted improvements in fecal counts of *Bifidobacterium* spp. and *Lactobacillus* spp., with reductions in pathogenic *Clostridium perfringens* (Ishihara et al., 2001). Sheep consuming a by-product rich in polyphenols (grape pomace) increased antioxidant mechanisms and improved their gut health through a suppression in the intestinal growth of pathogenic *Escherichia coli* and *Enterobacteriaceae* and an enhanced growth of facultative probiotic bacteria (Kafantaris et al., 2017).

Prophylaxis and self-medication

Continuous ingestion of small daily doses of PSC-containing foods in phytochemically rich forage environments entails a preventive strategy against disease referred to as feedforward (Vitazkova et al., 2001) or prophylactic self-medication (Villalba et al., 2014). It should be noted that prophylactic self-medication does not entail an associative learning mechanism. A major change in the study of medication has been the relaxation of the requirement that medicative behaviors should solely be directly detrimental to infectious agents (e.g., a direct antiparasitic, antifungal, antiviral or antibiotic effect) (de Roode and Hunter, 2019). On the contrary, hosts can be more tolerant or more resistant to disease through the antioxidant, antiinflammatory, immunomodulatory and prebiotic effects of dietary PSCs.

During prophylactic self-medication, animals consume low doses of PSCs as part of their diet in taxonomically and phytochemically diverse feeding environments. For instance, out of the 172 different plant species identified in the diet of Mahale chimpanzees, 22% contained PSCs that are effective at treating gastrointestinal-related illnesses in humans (Huffman, 1997). For ruminants, the bulk of any one meal is typically comprised of 3–5 plants, but they often eat small amounts of 50–75 plants during the day when foraging in diverse plant communities (Provenza, 2018). It is likely that the small doses of bioactives consumed with these minor dietary components have a positive effect on animal health. Indicators of animal health and welfare tend to increase when livestock graze diverse and phytochemically rich plant assemblages relative to monotonous pastures or feedlot diets (Villalba et al., 2017, 2019; Beck, 2020; Beck and Gregorini, 2020; Redoy et al., 2020; Garrett et al., 2021a,b). This may help explain why animals grazing taxonomically diverse and biochemically rich plant communities are in general more robust and tolerant to disease than those exposed to monocultures or rations with low to nil concentrations of plant bioactives (Provenza et al., 2019; Provenza et al., 2021). In fact, phytochemical richness—terpenoids, phenols, carotenoids, and tocopherols— in ruminant tissues increases with plant diversity relative to non-diverse pastures or grass monocultures (van Vliet et al., 2021), and this increment is associated to improvements in mitochondrial health, antioxidant and immunomodulatory activity with reduced inflammation in animals like bison (van Vliet et al., 2023). Collectively, prophylactic self-medication is amenable to emerge in environments where herbivores have the opportunity to consume a diversity of plants that contain antioxidant, prebiotic, antiinflammatory and immunomodulatory PSCs.

Prophylactic self-medicative behaviors also entail future needs for bioactives to be anticipated by the herbivore; it also implies that healthy individuals may experience temporary deviations from homeostasis through the consumption of not currently needed PSCs without negative impacts on their fitness (Beaulieu and Schaefer, 2013). However, in contrast to therapeutic self-medication, prophylaxis entails low to nil fitness costs to the herbivore, which could be attributed to the low doses of multiple PSCs ingested daily and/or to the storage and redistribution of PSCs within the organism in insects after ingestion (Beaulieu and Schaefer, 2013). Nevertheless, it is known that some antioxidants may function as pro-oxidants when ingested at high concentrations (Watjen et al., 2005), and that antioxidant supplementation in animals not challenged by oxidative stress may cause oxidative damage (Beaulieu and Schaefer, 2013). Thus, at certain thresholds of bioactive ingestion and as a function of physiological state, prophylactic chemical ingestion may also impose penalties to herbivores, similar to therapeutic self-medication. In fact, therapeutic self-medication through a selective increase in the use of dietary antioxidants (e.g., anthocyanins and flavonoids) has been reported in birds challenged by oxidative stress after long flights (Catoni et al., 2008) or during parasitic infections (Jiménez-Gallardo et al., 2023). Even when prophylactic self-medication may entail a cost, it could be inferred that such cost should be lower than taking the risk of suffering from disease and treating it therapeutically (Beaulieu and Schaefer, 2013). In summary, the paradox of the dual role of PSCs at reducing (i.e., as a toxin) or enhancing (i.e., as a medicine) fitness in both therapeutic and prophylactic self-medication can be understood through the balance between potential trade-offs between benefits and costs in healthy and sick individuals. It is also possible to hypothesize that the costs (e.g., in terms of negative impacts from PSCs or nutritional loses) impinged by therapy should be higher, i.e., due to greater doses and direct negative impacts on the infection, than the costs induced by prophylaxis.

Transgenerational learning and self-medication

Observational or social learning enhances learning efficiency because each animal does not need to discover the consequences to their behaviors just through trial and error. Thus, social organization creates knowledge that is passed from one generation to the next about how to survive in a changing environment (Provenza and Villalba, 2006). Observational learning is the process by which an individual observes the behavior of others (i.e., the model), the consequences of that behavior, and later imitates such behavior (Bandura, 1977). Mammalian herbivores learn quickly which food to eat from social models such as the mother and they also learn by observing peers (Provenza et al., 1998). A mother's influence on the diet of her offspring begins in utero (Nolte et al., 1992), continues through the chemical composition and sensorial characteristics of her milk (Nolte and Provenza, 1992), as flavors experienced by the offspring in these contexts are more readily accepted later in life (Provenza et al., 1998). The mother is particularly important as a young animal begins to forage prior to weaning (Chapple and Lynch, 1986; Thórhallsdóttir et al., 1990).

As for individual self-medication, research on the African great apes has unveiled key principles for understanding the role of social learning on self-medicative behaviors. Adult and healthy chimpanzees in proximity to sick individuals chewing the bitter pith of the medicinal shrub *Vernonia amygdalina* very rarely show interest in ingesting the pith themselves. However, infants of ill mothers have been seen to observe and taste small amounts of the pith discarded by their mothers (Huffman, 2016), suggesting a vertical transmission of knowledge from mother to offspring. Likewise, chimpanzees in the wild swallow folded rough hairy leaves of certain plant species (e.g., *Aspilia* spp.) as a means of physically expelling intestinal parasites (Huffman, 2001). The manifestation of this behavior is a function of the propensity these animals have to fold leaves. However, the acquisition and spread of the behavior as a function of parasitic infection within a group appears to be socially influenced from watching a model (family members or associates that are ill), and then evolving over time when the appropriate selective forces (e.g. parasite infection) are present, which allow the individual experience the positive feedback (e.g., relief from discomfort) brought about by leaf swallowing (Huffman and Hirata, 2004).

Preference by lambs for a medicine (polyethylene glycol-**PEG**) that attenuates the negative postingestive effects of quebracho tannins depended on the presence of the mother. Lambs exposed with either experienced or naive mothers to a feed high in tannins showed a much greater preference for PEG than lambs without their mothers (Sanga et al., 2011). In turn, the presence of lambs allowed naive ewes to learn the self-medicative behavior at a much greater rate than when ewes were exposed to tannins and PEG without their offspring (Sanga et al., 2011). Thus, the diffusion of the new self-medicative behavior occurred in both directions within the mother-offspring pair enhancing learning efficiency.

Pistacia lentiscus is a tannin-containing shrub with anthelmintic properties typically present in the diet of Damascus goats in the Mediterranean region at greater concentrations than in diets of Mamber goats, even when the shrub is equally available to both breeds. Under this context, Damascus goats appear to have adapted to a greater ingestion of PSCs and this has been associated with a lower prevalence/incidence of parasitic infections than that seen in Mamber goats (prophylaxis) (Amit et al., 2013). Nevertheless, it has been found that the greater propensity of Damascus goats to consume the shrub is learned from the mother as in a cross-fostering study, Mamber mothers educated Damascus kids to reduce their dietary consumption of *Pistacia lentiscus* to the low levels typically observed in the Mamber breed (Glasser et al., 2009). This study was the first to show in ruminants the influence of mother on prophylactic self-medication (in the absence of a parasitic infection). *Pistacia lentiscus* is a medicinal shrub that, as discussed above, may also impinge detrimental effects to the host (i.e., a cost). Thus, low levels of daily consumption of *Pistacia lentiscus* in the Mamber breed could be explained through the intake limitations that PSCs impose on herbivores. We hypothesize that mothers modulate these costs via their dietary habits and then influence *Pistacia lentiscus* use by their offspring. It is known in ruminants that the offspring's diet is influenced by what mother eats (Provenza et al., 1998), and that diet influences the gut microbiome (Youngblut et al., 2019; Zhu et al., 2021), which in turn have selective detoxification actions that modify tolerance to PSC-containing feeds (Dearing et al., 2022; Stapleton, 2022). Dietary habits and the taxonomic and functional core microbiome of Damascus goat mothers may allow a greater adaptation to PSCs and thus greater daily intakes of *Pistacia lentiscus*, which could facilitate prophylaxis. On the other hand, Mamber goat mothers with a diet that leads to a less adapted core microbiome may tend to consume tannins only when the benefits are much greater than the costs, i.e., therapeutic self-medication. In fact, Mamber goats have been found to more readily learn self-medicative behaviors when infected with endoparasites than Damascus goats (Glasser et al., 2009). In support of this idea, gorillas with a more diverse diet and a specialized gut microbiome with greater detoxification capacity than chimpanzees are more likely to ingest greater daily doses of unusual PSCs-containing plants (i.e., prophylaxis) than chimps. Chimps may take the risk of increasing their intake of PSCs when the cost is potentially lower than the benefit of treating parasitism (i.e., therapy) (Masi et al., 2012). Moreover, chimps relied more heavily on social information acquired by observing the fittest adults consume unusual PSC-containing plants (vertical knowledge transmission) than gorillas, which relied more on information gathered by observing related immatures (horizontal knowledge transmission). This difference has been explained through the greater risk in chimps to consume PSC-containing foods given their smaller body size and physiological ability to detoxify harmful compounds, and potentially less specialized gut microbiome with lower detoxification abilities (Masi et al., 2012). Regarding the latter, more recent studies suggest host diet is more influential than the host species at structuring the gut microbiome of chimps and gorillas (Campbell et al., 2020).

Phytochemical richness and interactions among plant secondary compounds

From the analysis on self-medicative behaviors described above it emerges that a diversity of plants and bioactives, strategically distributed in space and time will provide herbivores with the appropriate "raw materials" and opportunities to build diets that better prevent and treat disease (Fig. 1). As a first approach, we suggest more research is needed for understanding the prophylactic and therapeutic benefits of native and non-native and non-traditional forage species, as well as the specific bioactives and dose-responses underlying such functions. Under this context, it is important to simultaneously evaluate the potential detrimental impacts of these forages, as beneficial and harmful PSCs cannot always be consumed separately from natural forages. Secondly, an increment in medicinal plant diversity for monotonous landscapes entails a systematic study of plant adaptability and production responses to the climatic and soil conditions present at the different ecoregions where domestic ruminants live. In addition, an increase in chemical and taxonomic diversity may represent medicinal synergisms among multiple PSCs. Emphasis is typically given to single chemical isolates, potentially missing out on the benefits and harms of multiple combinations of PSCs (or combinations of multiple nutrients and PSCs), which may lead to amplified effects and enhance health benefits relative to single compounds (Vlaicu et al., 2023). Moreover, the synergistic effects of two or more medicinal PSCs entail lower doses of the combined components, which can reduce the penalties or costs described above for PSCs ingestion (Tallarida, 2011). In contrast, the possibility also exists that some PSCs may inhibit the effect of others (i.e., through chemical complexation; Copani et al., 2013), and thus the study of the combined medicinal benefits of different plant assemblages with their diversity of PSCs is recommended for managerial interventions aimed at enhancing animal health into the future.

Some polyphenols are being identified to have a wide range of synergistic effects in humans, from antioxidants and antimicrobials to anti-inflammatory, antidiabetic, and anticancer (see Mitra et al., 2023). Likewise, significant synergies against parasitic infections in sheep have been reported in a combination of medicinal plants containing alkaloids, condensed tannins, flavonoids and proteases, suggesting complex biochemical interactions that yield strong anthelmintic effects (Fomum and Nsahlai, 2019). Such interactions can be explained through additive effects, but also to non-linear effects that yield an amplified benefit. For instance, single plant extracts may show greater activity than their isolated chemicals suggesting a chemical synergism within the same plant. Extracts from *Artemisia absinthium* showed much greater antioxidant action than isolated sequiterpene lactones and flavones from the plant, suggesting other chemicals in the extract allow for strong synergistic actions (Gonzalez-Coloma et al., 2012). Likewise, essential oil extracts have been identified to have greater antibacterial activity than their major isolated components, suggesting chemicals at much lower doses in the natural matrix provide synergistic effects or potentiate the effects of single compounds (Burt, 2004). Moving into the future, the study of such chemical syner-

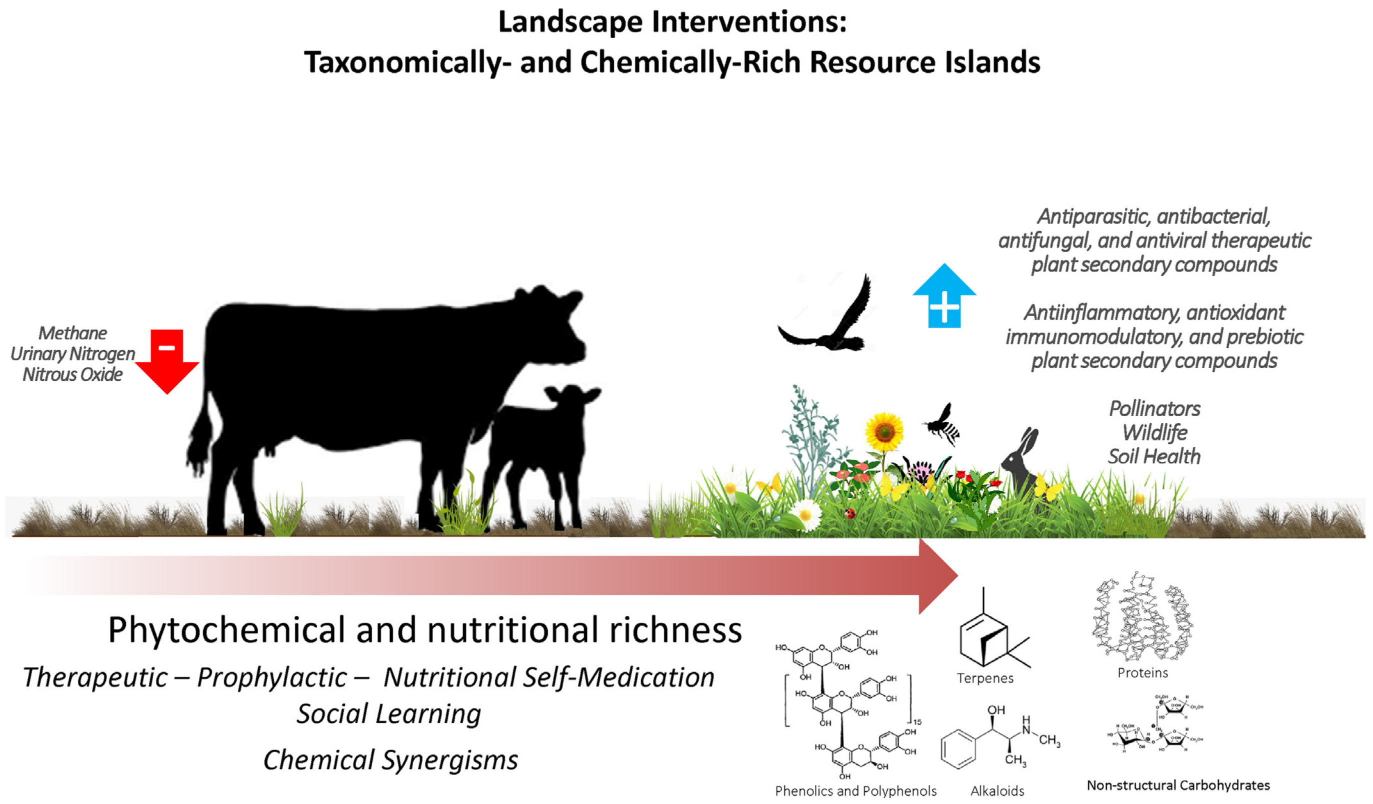

Fig. 1. The effects of landscape interventions on self-medication by domestic ruminant animals. Phytochemical and nutritional richness (red arrow) increases with the taxonomic diversity provided by focal resource patches or "islands" with a broad array of legumes, forbs and shrubs growing in a monotonous landscape. Such chemical and taxonomic richness enhances the likelihood of therapeutic, prophylactic and nutritional self-medicative behaviors. Social learning provides an adaptive advantage whereby animals can acquire such behaviors rapidly and efficiently. The likelihood of synergisms among multiple phytochemicals (e.g., plant secondary compounds – PSCs like phenolics, terpenoids and alkaloids) also increases with phytochemical richness. Islands of plant diversity may also promote reductions in enteric methane emissions, urinary nitrogen and nitrous oxide, enhancing pollinator and wildlife habitat, as well as soil health.

gisms will allow for the creation of functional landscapes that improve the efficiency and effectiveness for the treatment and prevention of disease.

Restructuring of rangelands and pasturelands with bioactive-containing forages

In many parts of the world, rangelands and pasturelands are typically dominated by a low diversity of monotonous grass species that peak briefly in nutritional quality in spring and early summer (e.g., 14–20% CP content, 65–80% *in vitro* organic matter disappearance), with declines (e.g., 2–6% CP content, 35–50% *in vitro* organic matter disappearance) in late summer through winter (Ganskopp and Bohnert, 2001). A low-quality nutritional environment decreases livestock performance and increases greenhouse gas emissions (Lee et al., 2017b; Cole et al., 2020) with very low to nil provision of medicinal and therapeutic inputs of PSCs to the grazer (Wooding et al., 2021). Importantly, reliance on low-quality forage grasses harms maternal nutrition and triggers epigenetic effects *in utero* that negatively impact fetal development and subsequent lifetime productivity of the offspring (Broadhead et al., 2019). Costly supplementation programs (e.g., hays, grains, urea, molasses), are in general implemented to prevent these deficiencies, but with very low to nil provision of PSCs and thus the lack of meaningful medicinal/prophylactic inputs to the animal is not resolved even after supplementation. Supplementation programs often amount to 35–40% of total variable production costs (Adams et al., 1996). Unfortunately, climate change and its negative impact on forage availability and nutritional quality will only add to the need for nutritional supplementation (Dumont et al., 2015; Augustine et al., 2018).

A reversal of these trends in dietary quality, diversity and phytochemical richness requires landscape interventions that aim at enhancing chemical and taxonomic diversity in the landscape. Legumes and forbs usually have greater protein and non-fiber carbohydrate content than grasses (Hall et al., 1999; Phelan et al., 2015). This contributes to enhanced herbivore nutrition and feed conversion efficiencies, thus reducing enteric methane emissions to the atmosphere (Cole et al., 2020), with the potential to promote shifts in macronutrient intake and facilitate nutritional self-medication as described above (Fig. 1). More importantly, many of legumes, forbs and shrubs contain PSCs with the medicinal, prophylactic and prebiotic activities described in this review to enhance animal health. In turn, phytochemical richness will enhance the likelihood of prophylactic and self-medicative behaviors through an increment in the rate of encounter of such chemicals in the feeding environment, allowing the animal the opportunity to build a diverse diet with the presence of bioactives (Fig. 1). Even very small inputs of nutrients and functional biochemicals from forages can deliver improvements in animal health (Beck and Gregorini, 2020; Beck, 2020). Thus, it is possible to restructure landscapes through the strategic distribution of relatively small patches of legume- and forb-rich "islands" that may synergistically complement the forage resource already available to herbivores (Fig. 1).

Resource islands can be viewed as nutrition centers and pharmacies where beneficial forages like legumes, forbs and shrubs are strategically established in the landscape as clusters, offering animals choices and opportunities for selecting greater amounts of biomass and nutrients, and for prophylactic and self-medicative behaviors. Once these behaviors are learned by mothers and peers, social transmission of self-medication will enhance learning efficiency, creating cultures within the herd that ingest a diverse diet that prevents and treats disease (Fig. 1). It is possible to devise scenarios where the monotony of a "sea of grass" is broken by the establishment of islands that provide a diversity of plant species with prophylactic chemicals for daily consumption, and other island patches with plant species that contain greater content of bioactives (i.e., and potentially less palatable plants like shrubs) that allow for therapeutic self-medication. Ruminants have spatial memory (Howery et al., 1999; Hewitson et al., 2005) and individual and social learning will facilitate the rate of encounter with these patches. In addition, grazing plans and the use of physical or virtual fences or herders may create managerial approaches that guide the ingestion of therapeutic and prophylactic doses of PSCs in grazing circuits across the landscape. This concept has been applied by French herders with the use of grazing circuits or rotations in rangelands to stimulate dietary diversity and enable sheep to select nutritious diets (Meuret and Provenza, 2015).

Beyond representing a significant source of nutrients and bioactives to herbivores, islands of plant diversity are expected to provide multiple ecosystem services, like cleaner air due to reductions in enteric methane emissions caused by dietary polyphenols (Mueller-Harvey et al., 2019) (Fig. 1). In addition, condensed tannins promote reductions in the route of N excretion to urine, favoring increments in fecal N, which is mainly in the organic form and has to be mineralized to ammonium before being susceptible to volatilization (Cai et al., 2017). Reductions in the proportion of N partitioned to urine are also beneficial for air and soils, as they constrain NH3 volatilization from urine and NO3— leached to groundwater and waterways (Leip et al., 2015). Moreover, condensed tannins in legumes inhibit N nitrification processes in soils, which mitigates soil N loss in pasture systems (Clemensen et al., 2020). Finally, reductions in urinary N ameliorate the production of the potent greenhouse gas N2O (Bao et al., 2018) (Fig. 1). Islands of diversity with their flowering plants and structural diversity can serve as refugia and corridors within monotonous landscapes by providing habitat (e.g., structural cover, insect populations), connectivity and resources for target plant and animal species (Fischer et al., 2014) (Fig. 1). Inputs of new forages may also contribute to healthy soils through increments in biomass and litter and aid in erosion control through root development (Gyssels and Poesen, 2003) (Fig. 1). Thus, the approach suggested creates multi-functional working landscapes (McGranahan, 2014) that benefit herbivores and the environment, making rangelands and pasturelands more resilient to climate change.

Restoration "islands" or plant patches are being used as a novel strategy to rehabilitate degraded and monotonous habitats efficiently and effectively in neotropical forests and some grassland ecosystems (see examples in Shaw et al., 2020). A fundamental premise under a restoration context is that these islands become sources of propagules that disperse outward across the degraded landscape through recruitment, facilitating recovery (Reis et al., 2010). Thus, the approach proposed for phytochemically diverse islands also represents a restoration tool for degraded habitats. The proposed benefits of the island approach include reducing management costs and increasing implementation feasibility relative to the traditional approach of seeding large areas with mixed swards across the landscape (Hulvey et al., 2017; Shaw et al., 2020). In addition, islands can serve as self-sustaining zones that restore and maintain ecosystem services and functions across the landscape. For instance, the establishment of native plants in highly invaded areas which reduces invasive dominance (Dechen Silva et al., 2019), or efforts at increasing taxonomic and/or structural heterogeneity in grasslands using strategic and focalized seeding techniques that enhance biodiversity, ecosystem services, habitat, and landscape aesthetics (Rayburn and Laca, 2013; Gornish et al., 2019). Moreover, by focusing their efforts on specific areas, managers can concentrate restoration resources in locales with greater potential for success (Hulvey et al., 2017).

The challenge ahead entails devising foodscapes and chemoscapes that facilitate in herbivores the opportunity to select the types and combinations of PSCs that allow and facilitate efficient nutritional, prophylactic and therapeutic self-medicative behaviors, creating cultures within herds that foster these behaviors trans-generationally. Transdisciplinary collaborations between agronomists, landscape architects, range scientists, nutritionists, behaviorists, land managers and ranchers could lead to integrated approaches. For instance, creating research that explores when, where, and which species and combinations to use, devising grazing plans to enhance behavior by consequences and social learning in animals grazing different landscapes, thus creating more sustainable, resilient and biodiverse systems.

An example on how to strategically deploy resource islands into the landscape and multidisciplinary collaboration is provided in

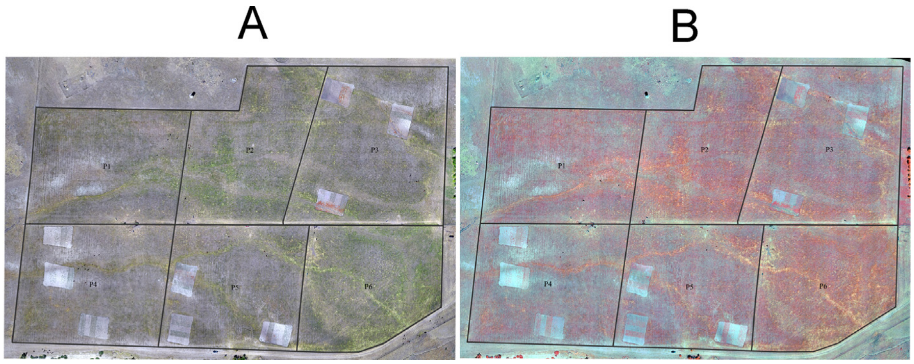

Fig. 2. A. Natural color orthoimage generated from imagery collected on 14 August 2023, using a DJI Mavic 2 Pro unmanned aerial system (UAS). The 22-ha grass (Meadow brome; *Bromus inermis*)-dominated pasture in northern Utah (111° 48′ 6″ W, 41° 53′ 22″ N) shows nine "islands" of 30 × 40 m (0.12 ha) each, distributed in three different fenced paddocks (P3, P4 and P5) (Treatment). The remaining paddocks (P1, P2, and P6), represent grazing areas without islands (Control). It is predicted that cattle (*Bos taurus*) grazing paddocks containing "islands" will increase animal performance, reduce enteric methane emissions, and improve immunological and antioxidant status relative to cattle grazing Control paddocks. Differences in color across the pasture represent variations in grass cover and species. B. Color infrared orthoimage generated from imagery collected by the same UAS filtered to the near infrared of the same pasture taken on 15 August 2023. Differences in color across the pasture represent variations in grass cover and species.

Fig. 2, where islands were established in a grass-dominated pasture. Geospatial scientists and rangeland ecologists located areas within the pasture for island establishment aiming at higher probabilities for seedling success and a spatial arrangement that optimized livestock distribution. To locate such sites, they focused on the premise that the limiting resource for plant establishment in semi-arid regions is water availability (Muñoz-Rojas et al., 2016; Zhang et al., 2020). Thus, areas within the pasture with a higher density or amount of vegetation were assumed to represent areas where moisture was greater (Dang et al., 2020; Yang et al., 2023). These areas were identified through a temporal sequence of satellite imagery that located pixels within a pasture whose greenness was higher than the average greenness of the pasture. Spatial groupings of these consistently greener pixels served as candidate locations for island establishment (Fig. 2). Plant scientists are then screening a wide variety of native and introduced plants for their establishment and persistence to aid in the selection of species to be seeded in those islands (Surbhi et al., 2023). Nutritionists and chemists are exploring chemical synergisms and nutritional complementarities among screened species. Cattle use of the different patches in the landscape will be assessed through GPS collars (Augustine et al., 2023). Beef cattle will be tested for the prophylactic benefits of grazing this combination of PSC-containing forages through blood markers of oxidative stress and mitochondrial metabolism, blood and urine phenolic metabolites (van Vliet et al., 2023), and blood immunoglobulins, interleukins, and TNF-α (Zhang and Zhao, 2022). It is predicted that grazing diverse foodscapes will increase animal performance, reduce enteric methane emissions, and improve immunological and antioxidant status in cattle. A greater forage diversity may also lead to more carbon storage in soils and an improved habitat for birds and pollinators.

Conclusions

Emerging results indicate that increasing the availability of bioactive-containing forages in rangelands and pasturelands has the potential to enhance animal health. Herbivores learn to prefer some of these bioactives (therapeutic self-medication) or modify their ingestion of nutrients (nutritional self-medication) when sick, whereas chronic and sustained consumption of bioactive-containing plants results in robust animals that are tolerant to disease (i.e., prophylactic self-medication). Social learning facilitates the emergence of such behaviors among conspecifics when alternatives, i.e., a diversity of plant species, are present across the landscape. Single forage species or grasses limit the ability of grazing or browsing herbivores to build a diet that maintains or improves health through prophylactic, therapeutic or nutritional self-medicative behaviors. Strategic distribution of nutritionally-dense and phytochemically rich forages in space and time could be integrated with knowledge about foraging principles to build new managerial dimensions in livestock production systems. In addition to the medicinal and nutritional inputs that maintain and restore health, landscape interventions that promote plant diversity will provide a broader array of services that significantly improve ecosystem sustainability and resilience to environmental disturbances.

Ethics approval

Not applicable.

Data and model availability statement

Not applicable. Data were not deposited in an official repository. No new datasets were created.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) did not use any AI and AI-assisted technologies.

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Declaration of interest

None.

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