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Phytochemicals in animal health: diet selection and trade-offs between costs and benefits

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Many plant tissues contain plant secondary compounds (PSC), which have long been recognised as defensive chemicals that deter herbivory via their toxic effects. However, herbivores may also benefit from including PSC into their diets. Plant-derived phenolics, terpenes and alkaloids have antiparasitic properties and sesquiterpene lactones have antibacterial, antifungal and antiparasitic properties. These actions are in part a consequence of the negative actions that PSC exert across several trophic levels, including the bacteria, parasites and fungi that inhabit herbivores’ bodies. Given the dual action, toxin and medicine, it is possible to hypothesise that self-selection of PSC by herbivores should occur when the benefits outweigh the costs of PSC ingestion. Recent research suggests that sheep and goats self-medicate against parasitic infections. They increase preference for condensed tannin-containing foods when experiencing a parasitic burden. This behaviour improves health; it is triggered by parasitism and weakens when parasitism subsides. However, the causes underlying these responses are not straightforward when viewed under a unidimensional cost–benefit analysis. This is because the intensity of antinutritional/toxic and medicinal effects of PSC is not static or just dependent upon the isolated post-ingestive effects of single PSC. Nutrient–PSC and PSC–PSC interactions, social models, as well as feeding patterns, all influence the perceived net benefit of incorporating medicines into a diet. A better understanding of the net benefit of self-medication in complex feeding environments will allow for the development of innovative managing strategies aimed at providing the food alternatives and conditions for improving the nutrition, health and welfare of grazing animals.

Self-medication: Plant secondary metabolites: Parasitism: Foraging behaviour: Condensed tannins

Many plant tissues contain plant secondary compounds (PSC), which have long been identified as chemical defences that deter herbivory via their toxic effects^(1,2). Despite their toxicity, intake of PSC by herbivores is a regulated process; by limiting how much of any one plant animals can eat, PSC protect plants from overuse by insects, birds, fish and mammals^(2–4). Diverse mixtures of plants with different types of PSC share the burden of tissue loss by causing herbivores to eat small amounts of a variety of species⁽⁵⁾. The term secondary compound

was coined by scientists who originally believed that these chemicals were waste products of the primary metabolism of plants. However, it is now known that the term is misleading as in addition to the benefits of preventing/reducing plant tissue loss to herbivores, PSC are essential for plants and herbivores with functions as diverse as attracting pollinators and seed dispersers⁽⁶⁾, protecting plants from ultraviolet radiation⁽⁷⁾ and defending plants and herbivores against oxidative stress, disease and pathogens^(8–11).

Abbreviation: PSC, plant secondary compounds.

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PSC are partitioned into three broad classes, phenolics, terpenes and alkaloids, each with thousands of compounds, making it difficult to make generalisations about their post-ingestive actions. However, it is known that condensed tannins, a tremendously diverse group of soluble phenolics, form complexes with a variety of chemicals, from proteins and carbohydrates to minerals and other PSC such as terpenoids, saponins and alkaloids⁽¹²⁾. Some of these interactions, particularly with proteins, explain some of the antinutritional effects of condensed tannins, such as the reported reductions of forage digestibility in ruminants⁽¹³⁾. In addition, some condensed tannins cause lesions in the gut mucosa⁽¹⁴⁾, and they can be degraded in the gut and absorbed, exerting their toxic actions systemically, impacting organs and physiological processes of herbivores^(15,16). Condensed tannins may also cause rapid and dramatic reductions in food intake, likely mediated by stimulation of the emetic system^(16,17).

Given the negative impacts of PSC on herbivores as a consequence of their role as chemical defences, it has been reasoned that PSC can exert similar actions across several trophic levels, including herbivores and the bacteria, parasites and fungi that inhabit herbivores' bodies and that cause decreases in health⁽¹⁸⁾. For instance, plant-derived alkaloids, terpenes and phenolics have antiparasitic and antimicrobial properties^(19–22) and sesquiterpene lactones have antiamebic, antibacterial and antifungal actions^(23–25). Since the pioneering work of Niezen *et al.*⁽²⁶⁾ in New Zealand with tannin-containing legumes, it is known that condensed tannins have anthelmintic properties, mainly through: (1) lower establishment of the infective third-stage larvae (L3) in the host, (2) lower excretion of eggs by adult worms and (3) impaired development of eggs into L3⁽²⁷⁾.

From the previous analysis, it follows that PSC may have a dual action on herbivores: a toxic/antinutritional effect derived from their inherent role as a chemical defence (i.e. cost) and a medicinal consequence (i.e. benefit), which could be explained by an extension of the protection that these chemicals impinge on plant tissues. In this review, we focus on mammalian herbivore–gastrointestinal parasite interactions as a model to explore herbivores' decisions in relation to the cost and benefits of PSC ingestion under the challenge of a parasitic burden. We believe that an enhanced predictive ability of the behaviour of herbivores faced with a trade-off between the medicinal and deleterious effects of PSC will allow for the creation of innovative management strategies aimed at enhancing animal health and welfare in animal production systems through self-selection of bioactive-containing plants or supplements. Mobilising the behavioural adaptation of herbivores to variation in their health status and in foods' characteristics, would allow to make animals more autonomous relative to their individual parasitic loads and to reduce chemical treatments, in accordance with agroecological principles⁽²⁸⁾.

Herbivore self-medication: costs *v.* benefits

From the previously described dual action of some PSC it is possible to hypothesise that the preference for foods

containing such compounds will be dictated by the 'resultant vector' of two opposing forces: toxic/antinutritional *v.* medicinal/curative effects. This 'resultant vector' is a function of the intensity of the effects of PSC on the herbivore and on the parasite in the tri-trophic interaction plant–herbivore–gastrointestinal parasite. When the intensity of medicinal effects of PSC outweighs the intensity of negative consequences on the fitness/performance of the herbivore, then self-selection of PSC is expected⁽²⁹⁾. In fact, it has been proposed that self-selection of PSC should: (1) improve fitness in sick animals, (2) decrease fitness in healthy animals and (3) be triggered by need, i.e. emerge as a consequence of infection⁽³⁰⁾. These criteria have been shown to be satisfied in insects consuming pyrrolizidine alkaloid-containing foods⁽³⁰⁾ and in primates ingesting bioactive (sesquiterpene lactones and steroid glucosides)-containing plants⁽³¹⁾. Longer-term studies are needed to assess potential fitness benefits in parasitised livestock offered PSC-containing foods. However, we know that self-selection of condensed-tannin containing foods is triggered by parasitism in sheep and goats and that such behaviour reduces parasitic burdens^(32–34). We also know that sheep reduce their preference for tannin-containing foods when parasitic burdens subside^(32,33) and that ingestion of condensed tannins induce penalties on performance (e.g. growth^(35–37)); see Table 1 for evidence of self-medication in animals).

If the medicinal actions of a PSC are less intense than its toxic/antinutritional activity, then parasitised herbivores are expected to experience a net cost from PSC consumption and thus avoid the PSC-containing food⁽²⁹⁾. For instance, the antinutritional effects of condensed tannins extracted from the Quebracho tree outweigh medicinal benefits when dosed at 8% of food intake, as observed by reductions in parasitic burdens in addition to reductions in performance by treated animals relative to controls that did not receive the PSC⁽³⁶⁾. This study did not assess diet selection as animals received a predetermined dose of condensed tannins with their diets, but a reduction in preference for the medicine is predicted in this context.

Finally, if the medicinal actions of a PSC are as intense as its toxic/antinutritional activity, no net benefit or cost is expected from selecting PSC-containing foods. Studies on parasitised sheep show that self-selection of tannin-containing foods does reduce parasitic burdens without a clear improvement of performance over control parasitised sheep^(32,33). It is likely that these studies were not long enough to observe a benefit on body weight gains or that the fitness benefits underlying preference were not necessarily linked to performance. Moreover, the intensity of the cost and benefits experienced by parasitised herbivores ingesting PSC may not just emerge from the isolated medicinal or toxic/antinutritional impacts of PSC on the host. Foraging behaviour is a multidimensional process^(38,39) where concentrations and types of nutrients and PSC vary across time and space and interact within the animal's diet.

Table 1. Studies showing evidence of self-selection of plant secondary compounds (PSC) aimed at improving health

Animal	PSC	Effect	Reference
Primates			
Chimpanzee (<i>Pan troglodytes schweinfurthii</i>)	Sesquiterpene lactones and steroid glucosides	Antiparasitic, antiamoebic, antibacterial, antifungal, antitumour	Huffman & Seifu ⁽⁵⁴⁾ ; Ohigashi <i>et al.</i> ⁽⁵⁵⁾
Insects			
Monarch butterflies (<i>Danaus plexippus</i>)	Cardenolides	Antiparasitic	Lefèvre <i>et al.</i> ⁽⁸⁹⁾
Woolly bear caterpillars (<i>Grammia incorrupta</i>)	Pyrrolizidine alkaloids	Antiparasitic	Singer <i>et al.</i> ⁽³⁰⁾
Tiger moths caterpillars (<i>Grammia geneura</i>)	Pyrrolizidine alkaloids	Antiparasitic	Bernays & Singer ⁽⁹⁰⁾
Birds			
Blackcaps (<i>Sylvia atricapilla</i>)	Flavonoids	Antioxidant, antiinflammatory, immunomodulatory	Catoni <i>et al.</i> ⁽⁹⁾ ; Beaulieu <i>et al.</i> ⁽⁶³⁾
Gouldian finch (<i>Erythrura gouldiae</i>)	Polyphenols	Antioxidant	Catoni <i>et al.</i> ⁽⁶²⁾
Ruminants			
Sheep (<i>Ovis aries</i>)	Condensed tannins	Antiparasitic	Villalba <i>et al.</i> ⁽³²⁾ ; Juhnke <i>et al.</i> ⁽³³⁾ ; Copani <i>et al.</i> ⁽⁵⁹⁾
Goats (<i>Capra hircus</i>)	Condensed tannins	Antiparasitic	Amit <i>et al.</i> ⁽³⁴⁾

Nutrients shaping the intensity of costs and benefits during self-medication

PSC are not consumed in a vacuum, they are ingested with other chemicals during a meal which in turn interact with the herbivore's physiological processes, feeding patterns and prior experiences with foods^(40,41). All these interactions can modify the potential benefits and penalties that different chemicals impinge on herbivores. Thus, it is difficult to depict a scenario where the resultant between the unidimensional and isolated effects of PSC as toxins or medicines dictate fitness benefits and as a consequence self-medication.

The complexity of interactions between nutrients and PSC can be simplified in a series of graphs in a two-dimensional space⁽⁴²⁾, where one dimension is a nutrient (nutrient axis) and the other a PSC that provides medicinal effects (PSC axis). The rationale of this system, the geometric approach, is rooted in behavioural homeostasis. When herbivores are offered choices among foods with different concentrations of nutrients and PSC with medicinal properties, their selection should reflect the outcome of homeostatic regulation for the chemicals in question^(43,44). This approach allows the animal to indicate how it prioritises the ingestion and utilisation of different food components and treats the interactions among such components as the primary variable. Moreover, the method enables measurement and interpretation of trade-offs reached between overeating some chemicals and undereating others, allowing for integration across different levels of biological analysis, including causation, development and evolution⁽⁴⁵⁾.

Nutrients influence the costs and benefits of self-medication in parasitised animals because it is known that an improved protein nutrition increases resistance to parasitic infections, i.e. an enhanced immunity to parasites⁽⁴⁶⁾. Consistent with this, sheep infected with gastrointestinal parasites select a diet with greater protein content than non-parasitised animals^(47,48). Likewise, caterpillars alter their feeding behaviour in response to

a viral or a bacterial infection by increasing their relative intake of protein compared with healthy controls or individuals dying of infection^(49,50). This behaviour shows a compensation for the protein costs associated with resistance (i.e. mounting an immune response) against pathogens. Some condensed tannins improve protein nutrition in ruminants, which in turn enhance immune responses to parasites⁽⁵¹⁾. Condensed tannins shift the site of protein digestion from the rumen to the intestines increasing the proportion of limiting and branched-chain amino acids reaching the small intestine^(52,53). Thus, condensed tannins may not always cause antinutritional effects on ruminants; on the contrary, they may improve protein nutrition⁽¹¹⁾ in addition to their anthelmintic effects. It is thus possible to hypothesise that parasitised herbivores will attempt to incorporate greater amounts of both protein-based foods and condensed tannins into their diets than healthy individuals. However, research is needed to determine how mammalian herbivores will trade-off protein-based foods and PSC-containing foods with PSC-free foods of lower protein but greater energy content, in a range of concentrations of PSC and nutrients. Indeed, the global ratio of costs (antinutritional/toxic effects) to benefits (anthelmintic effects and better protein nutrition) of a given food will depend on the concentrations of PSC and nutrients in that food.

Applying the geometric approach to available studies on livestock self-medication^(32,33) it is observed that parasitised animals trained to associate condensed tannin-containing foods with recovery from parasitic burdens select more condensed tannins, but less protein than control animals with a similar selection of digestible energy in the diet (Fig. 1). As predicted by Hutchings *et al.*⁽²⁹⁾ animals in these studies appear to be balancing the short-term cost of greater PSC intake (and lower nutrient intake) with the potentially longer-term costs that would have been incurred through greater parasitic loads if lower amounts of PSC were consumed. This was observed in naive parasitised animals, which selected lower amounts of Quebracho tannins than experienced parasitised animals

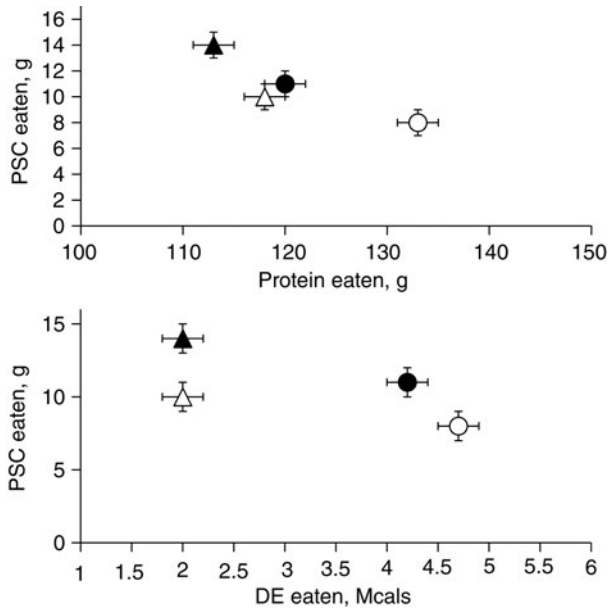


Fig. 1. Plots of mean protein, digestible energy and plant secondary compounds (PSC) (condensed quebracho tannins; PSC) intake during self-medication studies where sheep could select between a PSC-containing food and a PSC-free food. \triangle : naive control animals; \blacktriangle : parasitised animals (data taken from Villalba *et al.*⁽³²⁾). \circ : naive control animals; \bullet : parasitised animals (data taken from Juhnke *et al.*⁽³³⁾).

(treatment), the latter being trained to associate the ingestion of condensed tannins with relief from the parasitic infection⁽³³⁾. Nevertheless, the costs incurred by selecting more PSC in treatment animals were only transient as ingestion of the PSC-containing food was cyclic across days (see, e.g. Juhnke *et al.*⁽³³⁾), a temporal feeding pattern that may have maximised the medicinal effects of PSC, while minimising the toxic/antinutritional effects of these compounds (see the following section).

Feeding patterns shaping the intensity of costs and benefits during self-medication

Ingestion of medicines by parasitised animals is not constant across time. Once ingestion of PSC reduces infection, animals may then switch to a PSC-free diet, thus reducing the penalties induced by the toxic/antinutritional effects of PSC⁽²⁹⁾ and by the lost opportunities of harvesting more nutrients instead of a nutrient-diluted PSC-containing food. In support of this view, parasitised sheep displayed high use of tannin-containing foods only during certain days of the study. During other days, animals increased preference for the tannin-free alternative^(32,33). Likewise, wild chimpanzees self-medicate by selecting the bitter pith of the plant *Vernonia amygdalina* when suffering from parasite-related diseases⁽⁵⁴⁾. This medicinal plant contains toxic sesquiterpene lactones and steroid glucosides with antiparasitic activity at the doses consumed by the animals⁽⁵⁵⁾. However, and likely

due to the toxic effects of these PSC, the plant is sought with a low frequency, with a typical cyclic pattern of use across time, despite its year-round availability. This feeding pattern likely maximises the effectiveness of the medicinal actions of sesquiterpene lactones and steroid glucosides while minimising their severe toxic effects. Other studies also point to the ability of ruminants to balance the nutritional and toxicological effects of foods. Lambs offered a choice between a forage with high content of protein and ergovaline (a toxic PSC) or the same forage, but with lower concentrations of both protein and ergovaline, preferred the former at the beginning of the study, but then this pattern waned and by the end of the experiment they ate greater amounts of the latter food alternative⁽⁵⁶⁾.

Plant secondary compounds shaping the intensity of costs and benefits during self-medication

PSC interact with other PSC ingested in the diet, by a mechanism which may modify the intensity of their medicinal or toxic actions on the animal's body. It has been hypothesised that PSC ingested as a dilute mixture are less toxic to herbivores because they are less concentrated and potentially detoxified by different pathways⁽⁵⁾. In addition to PSC dilution, consuming a diversity of PSC may reduce the overall toxic effect of the mix, as the formation of gastrointestinal complexes could reduce the absorption and activity of single PSC^(5,57). As an example, intestinal bonding of tannins and saponins may result in moderated toxic effects⁽⁵⁸⁾ and condensed tannins in sainfoin complex ergot alkaloids from endophyte-infected tall fescue⁽⁵⁷⁾. Thus, gastrointestinal complexation represents a mechanism, which allows herbivores to consume more nutrients when offered diverse PSC-containing foods. Consistent with this, parasitised lambs ate more when allowed to select from saponin- and tannin-containing foods than when given access to either food alone. However, sheep offered choices experienced greater parasitic burdens than sheep offered single PSC-containing rations⁽⁵⁹⁾. The geometric approach applied to this study shows that the decision by animals offered choices was to harvest more protein and digestible energy and lower total amounts of PSC than animals fed either tannin- or saponin-containing foods (Fig. 2). This decision entailed a cost: greater parasitic burdens. However, the benefit for animals exposed to a choice between saponin- and tannin-containing foods paid off as it involved better performance than animals fed single PSC⁽⁵⁹⁾.

Flavonoids (e.g. flavonols, flavones and anthocyanidins) and other phenolic compounds (e.g. gallic acid, chlorogenic acids and stilbenes) synthesised to protect plants from oxygen free-radicals produced in photosynthesis provide antioxidant, antiinflammatory and immunomodulatory activities to herbivores^(21,60,61), which may be ingested as a diverse array of chemicals in a diet. Recent research suggests birds self-medicate with antioxidants⁽⁶²⁾. Birds challenged by an increased production of reactive oxygen species after long flights⁽⁹⁾ or under thermal stress⁽⁶³⁾ preferentially select foods high in flavonoids

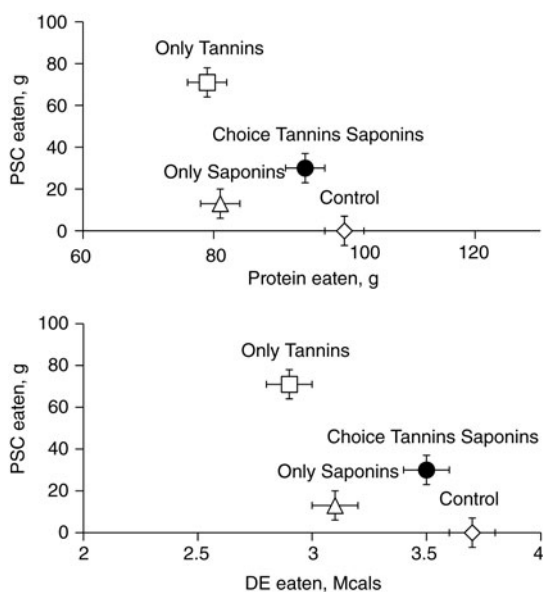


Fig. 2. Plots of mean protein, digestible energy and total plant secondary compounds (PSC) (condensed Quebracho tannins, saponins; PSC) intake during a self-medication study where parasitised groups of lambs were fed: (1) tannin-containing food (□; only tannins), (2) saponin containing food (△; only saponins), (3) PSC-free food (◇; control) or (4) choice between a tannin- and saponin-containing foods (●; choice tannins saponins). Data taken from Copani *et al.*⁽⁶⁹⁾

to attenuate the oxidative damage induced by the stressors while experiencing a concomitant increase in humoral immunity (benefits). However, more research is needed to evaluate the costs or penalties incurred by antioxidant ingestion under the presence and absence of an oxidative challenge. For instance, ingestion of antioxidants by red-winged blackbird chicks experiencing a low production of reactive oxygen species leads to an increased oxidative damage, while the opposite pattern is observed when supplementing antioxidants to chicks challenged by oxidative stress (see Beaulieu & Schaefer⁽⁶⁴⁾). Moreover, the penalties incurred by antioxidant consumption are recognised in human subjects, as antioxidant use is only recommended for individuals in a suboptimal oxidative state (see Beaulieu & Schaefer⁽⁶⁴⁾). Polyphenols may act as pro-oxidants at high doses with potential negative impacts on biomolecules such as DNA, proteins and lipids^(65,66) and toxicity can occur at high intake levels of some commonly consumed antioxidants⁽⁶⁷⁾. Thus, it appears that as other PSC involved in self-medication, antioxidants: (1) improve fitness in sick animals, but (2) may decrease fitness in healthy individuals.

Experience shaping the intensity of costs and benefits during self-medication

Herbivore experience with PSC may influence mammalian gut microbial communities in a way that favours

those microbes associated with enhanced detoxification and tolerance^(5,68). For instance, adding PSC to woodrats' (*Neotoma bryanti* and *Neotoma lepida*) diets altered gut microbial community structure, being the response a function of the animals' prior experiences with ingesting PSC⁽⁶⁹⁾. In addition, mammals and insect herbivores modify the production enzymes in their tissues that detoxify PSC, including cytochrome P450, as a function of their previous exposure to PSC^(70,71). Thus, experience has the potential to modulate the intensity of penalties associated with PSC ingestion, and as a consequence, preference for PSC-containing foods. As an example, lambs exposed early in life to foods containing oxalates, terpenes and condensed tannins consume substantially greater amounts of these foods later in life than naive animals, even when alternatives of greater quality were available for consumption^(72,73). The diverse microbial populations present in the foregut of ruminant herbivores can lead to several metabolic biotransformations that alter PSC, thus influencing the biological activity of these chemical compounds as exposure increases⁽⁷⁴⁾, likely to a greater extent than for monogastric animals. For instance, gradual exposure to increasing levels of oxalic acid to ruminants leads to a change in the composition of the rumen microbial population, which results in the breakdown of oxalic acid⁽⁷⁵⁾. Chronic exposure to terpenes in sheep increases their ability to consume terpenes⁽⁷⁶⁾ as rumen microbes adapt to monoterpenes⁽⁷⁷⁾ and diterpene diesters⁽⁷⁸⁾. Collectively, past experiences and environmental contexts that encourage exposure to different PSC-containing foods help explain the contrasting patterns of PSC intake, and tolerance, observed among different groups of animals, even when they belong to the same species.

Goats of the Damascus breed typically show a high propensity to consume a tannin-containing shrub, *Pistacia lentiscus*, with anthelmintic properties, even when parasitic burdens are not a concern. In contrast, healthy goats of the Mamber breed incorporate much lower amounts of *P. lentiscus* into their diet⁽³⁴⁾. The contrasting use of this medicinal plant between breeds appears to be learned, as a cross-fostering study showed that Mamber mothers educate Damascus kids to use low amounts of *P. lentiscus* in their diets⁽⁷⁹⁾. Moreover, the different use of *P. lentiscus* by the two breeds influences the amount of PSC that animals are willing to incorporate into their diets when experiencing a parasitic burden. When given a choice between *P. lentiscus* and hay, parasitised goats of the Mamber breed showed a greater preference for the medicinal plant than non-parasitised counterparts, a response which was not found in Damascus goats⁽³⁴⁾. *P. lentiscus* is a medicinal shrub (benefit) but also induces detrimental effects on protein metabolism (cost) in the absence of disease⁽³⁴⁾. Damascus goats, typically show a higher propensity to consume *P. lentiscus* and thus they regularly consume, and tolerate, greater amounts of PSC in their diet. This feeding pattern likely optimises the benefit:cost ratio of ingesting the toxic shrub even when animals are not infected, i.e. adopting a prophylactic way of self-medication (see later). Conversely, the Mamber goats,

which are less tolerant to the PSC present in the shrub as a consequence of their typical lower exposure to this food resource, use this plant therapeutically, i.e. when triggered by a parasitic burden. This example gives insights into how contrasting experiences with PSC-containing foods, or contrasting experiences among herbivores, may influence the intensity of costs and benefits in animals and as a consequence self-medicative behaviour.

Diluting the costs of plant secondary compounds: feedforward mechanisms and selection of medicinal foods with low toxicity

The costs of PSC ingestion can be minimised in herbivores by the sustained ingestion of a diversity of medicinal PSC at low doses with diet. In addition, and as described earlier, PSC ingested as a dilute mixture are less toxic to herbivores because they are less concentrated and potentially detoxified by different pathways⁽⁵⁾. Chronic ingestion of small daily doses of PSC in a dietary context involves a health preventive strategy which has been referred to as feedforward⁽⁸⁰⁾ or prophylactic self-medication⁽⁸¹⁾. This behaviour likely exerts minimal to nil costs on animals with potential long-term benefits. Consistent with this, diets of some wildlife species or of human cultures contain a high diversity of PSC-containing plants where PSC are consumed in low doses but on a daily basis. For instance, 30 % of the daily herbaceous diet of mountain gorillas, contains PSC with antibacterial properties. Of the 172 plant species typically consumed by Mahale chimpanzees, 22 % are used to treat gastrointestinal-related illnesses in human subjects. In addition, 89 % of the species used to treat symptoms of malaria among the Hausa people in Nigeria are also used in their diets⁽⁸²⁾. Dietary habits in human subjects play a crucial role at ensuring proper and regular consumption of preventive chemicals such as antioxidants^(83–85).

Mammalian herbivores selecting certain PSC or arrays of PSC in their diets may incur in low to nil costs when toxicity of the PSC at moderate doses is inherently low or nil and when PSC provide additional benefits such as those described for condensed tannins on protein nutrition. For instance, most temperate tannin-containing fodder legumes naturally growing in permanent pastures, such as sainfoin (*Onobrychis viciifolia*) or birdsfoot trefoil (*Lotus* spp.) species are characterised by moderate concentrations of condensed tannins, ranging from 0.4 to 8 % as a function of different phenological stages or growths⁽⁸⁶⁾. At intermediate condensed tannin concentrations (3–5 %), sainfoin then brings benefits in terms of nutritive value (similar to non-tannin-containing legumes such as alfalfa⁽⁸⁶⁾) while still providing antiparasitic actions⁽⁸⁷⁾. In these conditions, herbivores may not need to balance the beneficial effects of sainfoin (i.e. nutritional and medicinal) against the ingestion of PSC as they benefit from selecting sainfoin over other tannin-free forages regardless of their level of parasitic burden. Thus, the inherent beneficial characteristics of some medicinal plants may not satisfy the second criterion described by Singer *et al.*⁽³⁰⁾ needed to identify self-selection of PSC

by parasitised individuals: a decrease in fitness by healthy animals. In a recent experiment, we offered parasitised and non-parasitised lambs a choice between two types of sainfoin pellets characterised by their level of tannin concentration (low, 2 % *v.* moderate, 4 %)⁽⁸⁸⁾. Initially, both groups preferred the low-tannin sainfoin pellets (74 % preference) suggesting that the concentration of condensed tannins led to an initial rejection of the food type with a greater content of condensed tannins. However, after a 3-week period of exposure to only sainfoin pellets containing 4 % condensed tannins, preference reversed and all lambs preferred (62 %) sainfoin pellets with 4 % condensed tannins over pellets with lower condensed tannin content. Hence, the experience lambs had with sainfoin at moderate tannin concentrations likely optimised the benefit:cost ratio during choice tests, increasing lambs' propensity to include a greater concentration of condensed tannins into their diet. Both parasitised and non-infected lambs displayed the same pattern of preference for tannin-containing pellets, suggesting that the benefits of condensed tannins were not only circumscribed to their anthelmintic benefits, but also to other advantages such as nutrient supply with low to nil penalties to the host, a process consistent with prophylactic self-medication.

Conclusions

Concentrations and types of medicines, nutrients and PSC vary across time and space, creating a multidimensional feeding environment. Likewise, herbivores' experiences and feeding patterns change in time and space as well as the interactions among chemicals in a diet. This complexity hinders potential unidimensional explanations about the cost and benefits of ingesting medicinal, and potentially toxic, PSC. A better understanding of the rewards and penalties emerging by the ingestion of specific PSC interacting with other chemicals in the diet (nutrients, PSC) and with time, as well as with past herbivores' experiences with PSC and nutrients will improve our predictive ability regarding the fitness benefits associated with self-medication. This new knowledge will guide novel management approaches, which allow animals to 'write their own prescriptions' and build their own diet in diverse feeding environments with choices among plants, forages, supplements or rations with different concentrations and types of nutrients and PSC.

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Conflicts of interest

None.

Authorship

J. J. V., M. C. T. and C. G. co-wrote the paper and have primary responsibility for final content.

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